Approved by SACGHS 2-5-2010

This report will be sent forward to the Secretary of Health and Human Services following the incorporation of an executive summary and other prefatory material and copy editing.

Revised Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests

---

Secretary's Advisory Committee on Genetics, Health, and Society

ABOUT SACGHS

[TO BE DEVELOPED]

Approved by SACGHS 2-5-2010

This report will be sent forward to the Secretary of Health and Human Services following the incorporation of an executive summary and other prefatory material and copy editing.

COMMITTEE ROSTER

Chair

Steven Teutsch, M.D., M.P.H. (2010)
Chief Science Officer
Los Angeles County Department of Health
313 North Figueroa Street, Room 807
Los Angeles, CA 90012

Members

Mara Aspinall, M.B.A. (2011)
President and CEO
On-Q-ity
610 Lincoln Street
Waltham, MA 02451

Sylvia Mann Au, M.S., CGC (2010)
Hawaii State Genetics Coordinator
Genetics Program
Hawaii Department of Health
741 Sunset Avenue
Honolulu, HI 96816

Janice V. Bach, M.S.** (2013)
State Genetics Coordinator and Manager
Michigan Department of Community Health
Genomic and Genetic Disorders Section
201 Townsend Street
Lansing, MI 48909

Paul Billings, M.D., Ph.D., FACP, FACMG (2011)
Director and Chief Scientific Officer
Genomic Medicine Institute
El Camino Hospital
Mountain View, CA

David Dale, M.D. (2012)
Professor of Medicine
University of Washington
1959 NE Pacific Street
Seattle, WA 98195

Gwen Darien (2012)
Executive Director
Samuel Waxman Cancer Research Foundation
1249 Fifth Avenue, Suite 907
New York, NY 10029

Rochelle Dreyfuss, M.S., J.D. (2011)
Pauline Newman Professor of Law
New York University School of Law
Vanderbilt Hall, Room 333
New York, NY 10012-1099

Charis Eng, M.D., Ph.D.** (2013)
Chair and Founding Director
Genomic Medicine Institute
Cleveland Clinic Foundation
9500 Euclid Avenue., NE-50, Room NE5-314
Cleveland, OH 44195

James P. Evans, M.D., Ph.D. (2010)
Professor of Genetics and Medicine
Director of Clinical Cancer Genetics and the
Bryson Program in Human Genetics
Departments of Medicine and Genetics
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7624

Andrea Ferreira-Gonzalez, Ph.D. (2010)
Professor of Pathology and
Director of Molecular Diagnostics Laboratory
Virginia Commonwealth University
403 North 13th Street
Clinical Support Center Room 246
Richmond, VA 23298-0248

Julio Licinio, M.D. (2010)
Director
The John Curtin School of Medical Research
The Australian National University
Acton, ACT 0200
Australia

Barbara Burns McGrath, R.N., Ph.D. (2010)
Research Associate Professor
University of Washington School of Nursing
Box 357263
Seattle, WA 98195

Samuel Nussbaum, M.D.** (2012)
Executive Vice President
Clinical Health Policy
And Chief Medical Officer
Wellpoint, Inc.
120 Monument Circle
Indianapolis, IN 46204

Charmaine D. M. Royal, Ph.D. (2012)
Associate Research Professor
Institute for Genome Sciences and Policy (IGSP)
Duke University
450 Research Drive, Box 91009
LSRC B-Wing, Room 320B
Durham, NC 27708

Sheila Walcoff, J.D (2012)
Partner
McDermott, Will & Emery, LLP
600 13th Street, N.W., Suite 1200
Washington, DC 20005

Marc S. Williams, M.D., FAAP, FACMG (2010)
Director Intermountain Healthcare
Clinical Genetics Institute
324 10th Avenue. Suite 130
Salt Lake City, UT 84103

Paul Wise, M.D., M.P.H. (2011)
Richard E. Behrman Professor of Child Health and Society
CHP/PCOR
Stanford University
117 Encina Commons
Stanford, CA 94305-6019

*Terms expire in the year indicated in parentheses after the Committee Member's name
**Appointment pending

Ex Officios

Department of Commerce

Michael Amos, Ph.D.
Scientific Advisor
Chemical Science and Technology Laboratory
National Institute of Standards and Technology
100 Bureau Drive
Gaithersburg, MD 20899-8300

Department of Defense

LTC Adam Kanis, MC, USA
Tripler Army Medical Center
1 Jarrett White Road
MCHK-PE
Department of Pediatrics
Tripler AMC (Honolulu), HI 96859

Department of Energy

Daniel Drell, Ph.D.
Biologist
Life Sciences Division
Office of Biological and Environmental Research
Department of Energy
1000 Independence Avenue, SW
Washington, DC 20585-1290

Department of Health and Human Services

Naomi Goldstein, Ph.D.
Director
Office of Planning, Research, and Evaluation
Administration for Children and Families
370 L'Enfant Promenade SW, 7th Floor
Washington, DC 20447

Gurvaneet Randhawa, M.D., M.P.H
Medical Officer
Center for Outcomes and Evidence (COE)
Agency for Healthcare Research & Quality
540 Gaither Road
Rockville, MD 20850

Muin J. Khoury, M.D., Ph.D.
Director
Office of Public Health Genomics
Centers for Disease Control and Prevention
1825 Century Center Blvd, Suite 1000
Atlanta, GA 30345

Barry M. Straube, M.D.
Chief Medical Officer
Office of Clinical Standards & Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard, MS S3-02-01
Baltimore, MD 21244-1850

Alberto Gutierrez, Ph.D.
Deputy Director
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health
U.S. Food and Drug Administration
2098 Gaither Road
Rockville, MD 20850

Approved by SACGHS 2-5-2010

This report will be sent forward to the Secretary of Health and Human Services following the incorporation of an executive summary and other prefatory material and copy editing.

Denise Geolot, Ph.D., R.N.
Director
Center for Quality
Health Resources and Services Administration
5700 Fishers Lane
Rockville, MD 20857

Eric Green, M.D., Ph.D.
Director
National Human Genome Research Institute
Building 31, Room 4B09
31 Center Drive, MSC 2152
Bethesda, MD 20892

Robinsue Frohboese, J.D., Ph.D.
Principal Deputy Director
Office for Civil Rights
200 Independence Avenue, SW, Room 515F
Washington, DC 20201

Michael A. Carome, M.D.
Associate Director for Regulatory Affairs
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Michael A. Carome, M.D. (Acting *Ex Officio*)
Office of Public Health and Science

Department of Labor

Phyllis Borzi, J.D., M.A.
Assistant Secretary of Labor
Employee Benefits Security Administration
200 Constitution Avenue, NW, Suite S-2524
Washington, DC 20210

Department of Veterans Affairs

Ellen Fox, M.D.
Director
National Center for Ethics in Health Care
Department of Veterans Affairs
810 Vermont Avenue, NW
Washington, DC 20420

Equal Employment Opportunity Commission

Stuart Ishimaru, J.D.
Acting Chair
Equal Employment Opportunity Commission
1801 L Street, NW
Washington, DC 20507

Federal Trade Commission

Sarah Botha, J.D.
Attorney
Bureau of Consumer Protection
Division of Advertising Practices
Federal Trade Commission
600 Pennsylvania Avenue, NW, Room NJ-3212
Washington, DC 20580

ACKNOWLEDGMENTS

[TO BE DEVELOPED]

TABLE OF CONTENTS

PREFACE

SACGHS was first chartered in the fall of 2002 to formulate advice and recommendations on the range of complex and sensitive medical, ethical, legal and social issues raised by new technological developments in human genetics, including the development and use of genetic tests. One of the specific issues that the charter calls on SACGHS to examine is "current patent policy and licensing practices for their impact on access to genetic technologies." Accordingly, during the development of its first study agenda in 2003-2004, the Committee identified the role that gene patenting and licensing practices may play in patient access to genetic tests as a priority issue.

SACGHS' predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT),[1] also looked into the issue of the impact of gene patents on patient access. In 2000, following consultations with Government, industry, academia, legal experts, clinicians, ethicists, and patient communities, SACGT concluded that further data and analysis were needed to determine whether certain patenting and licensing approaches may be a) having adverse effects on access to and the cost and quality of gene tests; b) deterring laboratories from offering tests beneficial to patients because of the use of certain licensing practices; c) affecting the training of specialists who offer genetic testing services or d) affecting the development of quality assurance programs. In a letter to the Secretary of Health and Human Services, SACGT also acknowledged that gene patents can be critical to the development and commercialization of gene-related products and services. In an August 8, 2001, reply to SACGT, the Acting Principal Deputy Assistant Secretary for Health concurred with the need for additional data.

SACGHS' exploration of gene patents began in earnest in 2006 when the National Research Council (NRC) completed a study commissioned by the National Institutes of Health (NIH) on the granting and licensing of intellectual property rights on the discoveries relating to genetics and proteomics and the effects of these practices on research and innovation. The NRC report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health,*[2] was released in fall 2005 and published in 2006.

Because of the relevance of the NRC work, SACGHS thought it best to review its findings before proceeding further. After reviewing the NRC report, SACGHS agreed with its general thrust—particularly the conclusion that although the evidence to date suggests that the number of difficulties created for researchers by human DNA and gene patenting is currently small, the complexity of the patent landscape is worrisome and may become "considerably more complex and burdensome over time."[3] SACGHS also noted the report's recommendation that Federal research funding agencies should continue their efforts to encourage the broad exchange of research tools and materials.

[1] The Secretary's Advisory Committee on Genetic Testing (SACGT) was chartered between 1998 to 2002.
[2] NRC. (2006). *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health.* Washington, DC: National Academies Press.
[3] Ibid., p. 3.

Since the NRC committee's focus was on the effects of intellectual property practices on innovation and research rather than on clinical issues, SACGHS concluded that its work was of limited relevance to the impact of patents and licensing practices on patient access. Only one of its recommendations, in fact, dealt with the clinical dimension, and it pertained to a concern about the barriers that patents and exclusive licensees might represent to the independent validation of test results—a quality issue. SACGHS decided that more information was needed regarding the effects of gene patents and licenses on patient and clinical access to diagnostic and predictive genetic tests. At its June 2006 meeting, SACGHS held an informational session on gene patents. SACGHS formed a task force, composed of SACGHS members, nongovernmental experts appointed as *ad hoc* members, and technical experts from relevant Federal agencies.[4]

The task force's role was to guide the development of an in-depth study assessing whether gene patenting and licensing practices affected patient and clinical access to genetic tests, and if so, how. The study involved a review of the literature, the commissioning of original case studies, consultations with experts, including experts on gene patent policy in other countries, and the gathering of public perspectives.

The task force presented a public consultation draft report to the full Committee for review in December 2008. The draft report summarized the Committee's findings and conclusions from the commissioned case studies, literature review, and expert consultations and presented a range of policy options for public consideration. SACGHS agreed that the draft report should be released to the public for comment. After revisions were made to the report to reflect the Committee's discussion, the consultation draft was released for comment through the *Federal Register*, the SACGHS Web site, and the SACGHS listserv. The public comment period ran from March 9, 2009, to May 15, 2009.

In summer 2009, the SACGHS task force considered the public comments and developed a revised version of the report for the Committee's consideration. The revised draft report and proposed recommendations were extensively discussed by the Committee at its October 2009 meeting. The Committee made modifications to the recommendations and, with 14 voting members present, by an overall vote of 12 to one, with one abstention, approved the six recommendations. The Committee also called for further changes to be made to the report to incorporate a more extensive discussion of the public comments received during the public

[4]The Task Force consisted of experts with diverse perspectives, not all of whom necessarily agreed with all the conclusions and recommendations outlined in the report. The group had two chairs Debra G.B. Leonard, and after her SACGHS term ended, James P. Evans. The group's members were Mara Aspinall, Sylvia Au, Rochelle Dreyfuss, Andrea Ferreira-Gonzalez, all SACGHS members; Chira Chen, a patient representative, Joseph Telfair, a public health and consumer advocacy expert, and Emily Winn-Deen, an expert in gene diagnostic manufacturing, all former SACGHS members; and Brian Stanton, a patent and technology transfer policy expert. The technical experts from the Government were Scott Bowen, Deputy Director of the National Office of Public Health Genomics at the Centers for Disease Control & Prevention; Martin Dannenfelser, then-Deputy Assistant Secretary for Policy and External Affairs at the Administration for Children & Families; Claire Driscoll, Director of the National Human Genome Research Institute's (NHGRI's) Technology Transfer Office; Jonathan Gitlin, a science policy analyst with NHGRI; Ann Hammersla, Director of the Division of Policy of the NIH Office of Technology Transfer (OTT); John LeGuyader, Director of the USPTO's Technology Center 1600; Laura Lyman Rodriguez, Acting Director, NHGRI's Office of Policy, Communication and Education; and Mark Rohrbaugh, Director of NIH OTT.

consultation process and at the October meeting and to clarify the basis of the Committee's conclusions. The report was revised for presentation at the February 4-5, 2010, meeting. During the revision period, three members wrote a statement of dissent. It appears at the end of this report.

TO BE FURTHER DEVELOPED FOLLOWING THE OUTCOME OF THE FEBRUARY 2010 MEETING.

EXECUTIVE SUMMARY

[TO BE DEVELOPED]

INTRODUCTION

SACGHS' Longstanding Commitment to Technical Innovation and Access

The development and accessibility of validated, clinically useful genetic tests has been a central concern for the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) since its first meeting in June 2003. This concern has led the SACGHS to explore a variety of issues felt to be of central importance in determining the cadences of scientific discovery and the processes by which these discoveries are transformed into effective clinical and public health interventions. Coupled with this focus on supporting technical progress, SACGHS has also had a longstanding commitment to ensure equity in the availability of useful genetic tests and services and that they act to reduce, and not exacerbate, social disparities in health outcomes.

SACGHS has long recognized the need for federal policy to facilitate the development in both the private and public sectors of new genetic technologies and their application for improving human health. Accordingly, the Committee has published a series of comprehensive reports that recommend actions the Secretary can take to eliminate barriers to the development of reliable, effective tests and access to them. Reports that concern obstacles to the development of quality genetic tests include the Committee's 2008 report on the oversight of genetic testing, in which the Committee recommended specific improvements in federal regulatory policies as part of an effort to create a favorable environment for developing and assuring the quality of new genetic technologies. Also in 2008, the Committee issued a report on the promise of pharmacogenomics, which underscored the role of federal policies in facilitating private sector development of new technologies in this rapidly growing field.

While SACGHS' concern for the equitable provision of new genetic capabilities has been a primary consideration in all its deliberations and reports, the Committee addressed this issue directly in several ways. Reports focused on access to genetic tests include the Committee's 2006 report, "Coverage and Reimbursement of Genetic Tests and Services." In that report, the Committee identified steps the Secretary could take to reduce financial barriers to access to appropriate genetic technologies. In other communications with the Secretary, the Committee has consistently underscored the importance of equitable access to genetic tests and services as a means of advancing various health-reform goals, including reducing health disparities and improving public health. The Committee has also promoted access to genetic tests by strongly supporting efforts to prevent discrimination based on genetic information and seeking ways to expand the education and training of health professionals in genetics so that these professionals will adopt and appropriately use new genetic tests and services.[5]

The Relevance of Gene Patents and Licensing Practices to Patient Access

Given its concerns about the development of clinically useful, reliable genetic technologies and equitable access to these technologies, the Committee took note of reports in the literature discussing concerns that gene patents could create barriers that limited the development of these

[5] SACGHS Reports and Recommendations are posted on the SACGHS website at http://oba.od.nih.gov/SACGHS/sacghs_documents.html

tests, their quality, and patient access to them. The Committee also reviewed scholarly work suggesting that the dispersed ownership of gene patents might block the development of (and therefore access to) new multi-gene testing innovations. As a result, in 2004, the Committee formally identified as one of its priority topics the potential effects of patenting and licensing practices on genetic test development and patient access to genetic tests. While other agencies within the government are well positioned to consider issues of patentability, the Committee focused on the issues that arise after the patent issues, that is, on the effect issued patents have on patient access. In so doing, SACGHS was also fulfilling an explicit charge within its charter, namely to examine "current patent policy and licensing practices for their impact on access to genetic and genomic technologies."[6]

The importance of this priority topic has only increased in the years since 2004. During this time, genomic research has resulted in new insights into health and disease and created the potential for new genetic tests that may provide guidance to physicians in tailoring preventive strategies and treatments to individual patients. The importance of patents and licensing to the mandate of the SACGHS was reaffirmed in its assessment of the most important issues confronting federal policy on genetics and consequently, the central priorities for the Committee's deliberations for the coming year.[7]

Much is at stake with regard to gene patents and genetic testing, and controversy exists as to whether gene patents are promoting or blocking beneficial innovations in genetic testing and whether gene patents promote or restrict patient access to established genetic tests. Strongly held opposing viewpoints on these issues were expressed throughout the Committee's inquiry by members of the public, including clinicians, technology transfer professionals, industry representatives, and patient advocates.

The Committee recognized the controversies inherent in these issues as well as the difficulties in assessing these complex questions without more data. Therefore, a multi-pronged study plan was developed to address the following questions:

- whether patents and licensing practices are beneficial in promoting the development of and access to genetic tests; and
- whether patents and licensing practices are causing harm in terms of the quality of genetic tests, the availability of these tests to patients at reasonable prices, and the ability of clinical, research, and commercial communities to develop new or improved genetic tests.

A Comprehensive Analytical Approach

This study consisted of a literature review, consultation with experts, the solicitation of public comments, and original case studies. The case studies were conducted by the Center for Genome

[6] Charter for the Secretary's Advisory Committee on Genetics, Health, and Society. http://oba.od.nih.gov/oba/SACGHS/sacghs_charter.pdf

[7] See SACGHS Report on the Integration of Genetic Technologies Into Health Care and Public Health at: http://oba.od.nih.gov/oba/SACGHS/SACGHS%20Progress%20and%20Priorities%20Report%20to%20HHS%20Secretary%20Jan%202009.pdf

Ethics, Law & Policy, which is part of Duke University's Institute for Genome Sciences & Policy. The Center was selected in December 2006 for this work by the NIH Office of Biotechnology Activities (OBA), which provides staffing support for SACGHS, after consultation with the National Human Genome Research Institute's (NHGRI's) Ethical, Legal and Social Implications (ELSI) Research Program. The Center was selected because it was awarded a Centers of Excellence (CER) award—P50 HG 003391—specifically focused on research on genomics and intellectual property. The researchers at the Center, led by Dr. Robert Cook-Deegan, agreed to use the existing grant funds to conduct the case studies. While some of the researchers involved with this project receive salaries from Duke University, their salaries did not fund any of the research for the case studies. Overall, the focus of the Duke Center's research is to gather and analyze information about the effects of publication, data and materials sharing, patenting, database protection, and other practices on the flow of information in genomics research. The Center's work on this project also served NHGRI's interest in promoting research on intellectual property issues surrounding access to and use of genetic information. In particular, NHGRI is funding research that examines the impact of laws, regulations, and practices in the area of intellectual property on both the development and commercialization of genomic technologies and derived products and access to and use of such technologies and information by researchers and the public.[8]

The Center conducted eight case studies of 10 clinical conditions and the related patents and genetic tests for these conditions. The case studies were selected by the Duke group in consultation with the SACGHS gene patent task force and the full SACGHS Committee. Each case involves a Mendelian (inherited) disorder or a cluster of disorders associated with a clinical syndrome for which genetic tests are available. The case studies focused on:

1. inherited susceptibility to breast/ovarian cancer and colon cancer;
2. hearing loss;
3. cystic fibrosis (CF);
4. inherited susceptibility to Alzheimer disease;
5. hereditary hemochromatosis (HH);
6. spinocerebellar ataxias (SCA);
7. long QT syndrome (LQTS); and
8. Canavan disease and Tay-Sachs disease.

The cases were chosen in part because they involve different and contrasting patenting strategies and licensing schemes; they also include common and uncommon conditions. They include data from the literature and other sources regarding the effect of patents and licensing practices on the cost, availability, accessibility, and quality of particular genetic tests. The case studies were peer-reviewed, and subjects interviewed for the case studies had an opportunity to review draft case study reports and to correct factual inaccuracies.

The case studies cover developments that began more than a decade ago but also include very recent events. For example, the case studies' data on the price of genetic tests comes from a

[8] ELSI Research Priorities, NHGRI website, http://www.genome.gov/10001618.

survey of laboratories conducted in 2007 and 2008. The case study on LQTS covers the licensing situation before 2002 through the present. The study of access to genetic testing for hereditary breast, ovarian, and colon cancers includes events occurring as recently as 2009. The case study on Alzheimer disease covers new testing introduced in 2008. The CF case study discusses changes to medical practice in 2002, 2005, and 2006 that affect how intellectual property is used. The case study of hearing losses discusses business deals in 2008 and 2009 affecting intellectual property as well as the latest trends in technology platforms. The HH case study also documented changes in licensing practices between 2002 and 2008. A compendium of the eight case studies can be found in Appendix A of this report, and a summary box for each case study appears when the case study is first mentioned in the narrative of the report.

During the course of work on the case studies, and to complement the case study approach, the Duke investigators recommended that a second study be commissioned on the impact on technology development of licensing approaches under two different statutory frameworks for patenting and licensing: the Stevenson-Wydler Act, which applies to Federal laboratories, such as the NIH intramural research program, and the Bayh-Dole Act, which applies to Federal grantees and contractors. This work is still underway but preliminary results are summarized in Appendix 2 and further discussion appears later in this report. Duke University is funding the remaining work on this study through grant support.

SACGHS also gathered information and perspectives on a draft report through a solicitation of public comments that was published in the *Federal Register* and disseminated through the SACGHS Web site and the SACGHS listserv. The public consultation draft also asked for feedback on a broad spectrum of policy options, ranging from simply calling for stakeholder advocacy efforts to fundamental statutory changes that would apply to Government-owned and funded inventions as well as private sector inventions. The statutory options themselves ranged from making no changes to a prohibition on human health-related gene patents.

A total of 77 public comments were received on the public consultation draft report. Among the commenters were 11 professional associations, 16 technology transfer offices or technology transfer professionals, five academics, five health and disease advocacy groups, two industry trade groups, nine life science companies, nine health care providers, 4 commercial laboratories, and 12 private citizens.
In addition to these public comments, the Committee heard presentations from experts during the course of its study to gain a broad perspective on the topic. The experts included a patent attorney from a law firm; a federal technology transfer office attorney; an attorney with a company that makes products relating to genetic testing; an academic expert in policy issues relating to patents on genes; a judge with the U.S. Court of Appeals for the Federal Circuit, a federal court that has exclusive jurisdiction over appeals in patent cases; and several academics and a representative of the Organisation for Economic Co-Operation and Development who provided information on how international bodies and foreign countries have addressed concerns about patents on genes.

All of the information gathered through this multi-pronged study afforded the Committee an expansive view of the patent landscape for genetic tests—an outlook that enabled the Committee

to evaluate the issues it deemed important: that is, whether patents and licensing practices are overall beneficial or necessary in promoting the development of and access to genetic tests, and whether patents and licensing practices are causing harm in terms of the quality of genetic tests, the availability of these tests to patients at reasonable prices, and the ability of clinical, research, and commercial communities to develop new or improved genetic tests.

Developing Constructive Recommendations

The SACGHS mandate is to develop recommendations considered helpful in improving federal strategies to use genetic discoveries to improve human health. Therefore, the analysis of the benefits and harms associated with current gene patent and licensing policies were developed to inform the development of specific recommendations for the Department of Health and Human Services. However, before the Committee could formulate recommendations, it also had to consider patent law developments and determine whether these developments address or stand to address any identified problems. The Committee also reviewed U.S. technology transfer laws and policies to evaluate existing mechanisms for promoting a balance between access and innovation. Germane policy studies were also reviewed to evaluate the findings and recommendations of other groups. Finally, the Committee reviewed foreign patent laws to determine whether other countries' legal provisions provided a model for legal changes that could be recommended in the U.S.

The recommendations in this report call for focused changes designed to minimize observed harms in patient access, to eliminate barriers to test development and testing innovations, and to preserve benefits of gene patents for the development of genetically-based therapeutics. These recommendations reflect the considered judgments of the Committee based on all of the information gathered and its continued dual commitment to technical progress and equitable access to the technologies in a rapidly evolving health care environment.

Study Scope and Terminology Used in the Report

In previous reports, SACGHS has described the wide array of genetic tests currently in use, which rely on biochemical, cytogenetic, and molecular methods or a combination of these methods to analyze DNA, RNA, chromosomes, proteins, and certain metabolites.[9] The scope of this study and report, however, is on those genetic tests that rely on analysis of nucleic acid molecules to determine human genotype, whether used for diagnostic, predictive, or other clinical purposes. When the term "genetic test" is used in this report, it implies the broadest definition of nucleic acid tests, such as those called "genomic tests" or even whole genome sequencing, and is not limited to the single gene tests classically used for medical genetic diagnosis. The report does not address protein-based genetic tests or patent claims on isolated proteins.

Nor does this report explore questions about the legitimacy of granting patents on human genes or the morality of doing so—e.g., whether such patenting leads to the "commodification" of the

[9] In particular, see *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*.

human body. Other groups have explored this issue in depth,[10] and current court cases are pending that will address such matters. The Committee recognizes that many people have moral objections to gene patents, while many others see no fundamental moral issue or regard the benefits of patenting as outweighing other moral concerns.

The Committee gathered information on both *clinical access* and *patient access* to such tests. As used in this report, *clinical access* means the ability of a health care professional or laboratory to obtain or provide genetic tests for patients. *Patient access* means the ability of a patient to obtain genetic testing.

In some sections of the report, a distinction is made between laboratory-developed tests and genetic test kits. Laboratory-developed tests are tests developed by commercial and academic laboratories that are used to perform genetic testing as a clinical service.[11] References in the report to testing services should be understood as references to laboratory-developed tests. A genetic test kit is a physical diagnostic product that a laboratory could purchase and use to conduct testing. A laboratory that conducted its testing using a test kit purchased from a company is not using a laboratory-developed test. Even though a laboratory could use a purchased test kit to offer a testing service, references in the report to testing services refer only to laboratory-developed tests.

Another distinction between laboratory-developed tests and test kits is that they are currently subject to different oversight schemes. Test kits are subject to premarket review by the FDA. Most laboratory-developed tests are not subject to FDA review. Oversight of such tests is provided through the regulation of the laboratory conducting the tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Sections of this report also refer to multiplex testing, which involves the simultaneous testing of multiple genetic markers in a single test. Multiplex testing can involve testing one condition involving multiple markers or testing multiple conditions, with each condition determined by one or more genetic markers. More information on multiplex testing is provided later in the report. A multiplex test could be either a laboratory-developed test or a test kit.

The phrases "exclusive rights holder" or "patent rights holder," as used in this report, refer to the party that has rights to use and enforce the patent—this could be either the patent owner or the exclusive licensee.

Patent Law Basics and Types of Patents Associated with Genetic Tests

According to section 101 of the 1952 Patent Act, patents may be obtained for several types of inventions: processes (a series of steps "to produce a given result"[12]); machines (apparatuses[13]);

[10] Other reports have explored this issue in depth. ADD CITATIONS FOR OTA, Nuffield Council on Bioethics and the World Health Organization.,

[11] Examples of commercial laboratories include Myriad Genetics Laboratories, Inc., and Bio-Reference Laboratories, Inc.

[12] *Cochrane v. Deener*, 94 U.S. 780 (1877).

manufactures (articles made from raw or prepared materials but given new forms or properties[14]); compositions of matter (synthesized chemical compounds and composite articles[15]); and "any new and useful improvement thereof [a process, machine, manufacture, or composition of matter.]"[16] In addition to showing that the invention is patentable subject matter, the inventor must demonstrate that the invention is novel, useful, and nonobvious.[17] More information on what makes an invention nonobvious is provided in a later section. A patent provides a grant of "the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" until 20 years after the date of the patent application.[18]

The types of patent claims that can serve as the basis for exclusive rights to a genetic test generally fall into several categories. One category is compositions of matter/manufacture claims to isolated nucleic acid molecules. The claimed isolated molecules may have sequences that correspond to human genes, mutations, and fragments of the genes or mutations. An example of such a patent is patent 5,622,829, which claims cDNA (complementary DNA) forms of various tumorigenic *BRCA1* alleles and fragments of those alleles. Complementary DNA is DNA that has been made from the messenger RNA (mRNA) transcript of a gene. A cDNA sequence, like a mature mRNA sequence, differs from a gene sequence in that it lacks the non-coding regions of the gene. Because testing for the *BRCA1* mutated alleles typically involves using probes or primers that are fragments of those alleles, the patent holder's exclusive rights over the mutated allele fragments enables it to exclude others from performing testing. To avoid infringing these particular claims of the patent while testing for *BRCA1* mutant alleles, a test developer would have to devise a method of testing that did not use or make the claimed isolated fragments or alleles.

Patent claims to processes for the detection of particular nucleic acid sequences or mutations using probes, primers, or some other method are another category of patents that protect genetic tests. An example of a patent claim to a process or method of detecting a particular mutation associated with hearing loss is claim six of patent 5,998,147:

> A method of detecting a deletion of a guanosine at position 30 of the connexin 26 [*GJB2*] gene in a biological sample containing DNA, said method comprising:
>
> a) contacting the biological sample with a pair of oligonucleotide primers under conditions permitting hybridization of the pair of oligonucleotide primers with the DNA contained in the biological sample, said pair of oligonucleotide primers capable of amplifying a region of interest in the connexin 26 gene;
>
> b) amplifying said region of interest in the connexin 26 gene; and

---

[13] *Nestle-Le Mur Co. v. Eugene, Ltd.*, 55 F.2d 854 (6th Cir. 1932).
[14] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[15] Ibid.
[16] 35 U.S.C. § 101.
[17] These criteria are laid out in 35 U.S.C. §§ 101-103.
[18] 35 U.S.C. § 154.

c) detecting the deletion of a quanosine at position 30 of the connexin 26 gene.

Another example of a patent claim to a method of detecting a mutation is claim one of patent 5,753,441:

> A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

With patents such as these, the patent holder's exclusive rights to the method would be infringed by any genetic test that detects the designated mutation through the patented method.

Another category of patent claims that protect genetic tests are claims to processes involving simply associating a genotype with a phenotype. An example of such a patent claim is patent 5,693,470, which claims

> 1. A method of determining a predisposition to cancer comprising:
>
> testing a body sample of a human to ascertain the presence of a mutation in a gene identified as hMSH2 (human analog of bacterial MutS and Saccharomyces cerevisine MSH2) which affects hMSH2 expression or hMSH2 protein function, the presence of such a mutation indicating a predisposition to cancer.
>
> 2. The method of claim 1 wherein the sample is DNA.
>
> 3. The method of claim 1 wherein the sample is RNA.
>
> 4. The method of claim 1 wherein the sample is isolated from prenatal or embryonic cells.

The first claim, which does not specify a particular testing method, could be interpreted as giving exclusive rights to any method of testing that involves detecting the mutation and correlating it with cancer.

A significant distinction between composition of matter/manufacture claims to isolated nucleic acid molecules and method claims is that claims to molecules cover all uses of the molecule, including uses outside of diagnostics, while a claim to a method of using a molecule would not prohibit one from using that molecule for another method.

Other types of patents associated with genetic tests include claims to genetic test kits and claims to platform technologies used for genetic testing.

Throughout this report, where the Committee refers to "patent claims on genes" it means patent claims to isolated nucleic acid molecules whose sequences correspond to human genes, intergenic DNA (DNA located between genes), or mutations that occur in the human body; the phrase also refers to patent claims to methods of detecting particular sequences or mutations and claims to primers, probes, and other nucleic acid molecules useful for the detection of a particular gene, mutation, or sequence of importance. Where reference is made to "association patent claims," the Committee means patent claims upon the act of simply associating a genotype with a phenotype. Composition of matter/manufacture claims to isolated nucleic acid molecules that correspond to naturally occurring genes are commonly referred to as "gene patents," although this phrase, in some forms, can include patent claims upon the act of simply associating a genotype with a phenotype. For that reason, this report generally avoids the phrase "gene patents" in order to avoid confusion.

In some cases, a genetic test may be protected by multiple patent claims, including claims to DNA primer molecules, claims to methods of using fragment probes for mutation detection, and claims to methods involving the act of simply associating a genotype with a phenotype.

It is generally difficult if not impossible to "invent around" patent claims on genes and associations. Inventing around a technology involves making an invention that accomplishes the same thing as the original patented invention but that does not infringe the patented invention. To invent around patent claims on the ABC gene and fragments of that gene to create a genetic test for disease X, one might use probe or primer molecules corresponding to a second unpatented gene, DEF, associated with disease X. In this way, one would in theory have avoided using the patented molecules and still accomplished the end of the first invention—testing for disease X. However, such a strategy of utilizing only freely accessible genes in a diagnostic test without the ability to use the patent-protected gene would, by definition, result in an incomplete and clinically unacceptable test since all of those individuals with the disease who have a mutation in the patented gene would go undetected and undiagnosed. For a diagnostic test to be useful, it must encompass all (or at least most) of those particular genes associated with a disorder. A test that fails to assay even one gene that can cause a given disease is, by definition, an incomplete clinical test. Moreover, given the number of existing patents protecting genes, in some cases an unpatented substitute may not be available. In other cases, a particular gene or genetic marker that is patent-protected may well be the only unique sequence related to the underlying condition, eliminating completely the possibility to invent around it. Neither does existence of unpatented genetic markers in linkage disequilibrium to patented sequences provide a method for inventing around a diagnostic genetic test under patent protection as discussed later in the report. Finally, because association patent claims often claim a method of associating a particular genetic marker with a phenotype, in the absence of a substitute marker it is impossible to invent around an association patent claim.

A recent study confirms that a substantial number of patents relating to genetic testing will be difficult to invent around.[19] In that study, researchers from the Centre for Intellectual Property Rights and the Centre for Human Genetics in Belgium evaluated U.S. and European patent claims relating to genetic testing to see how many could be circumvented or invented around.[20] The researchers reviewed patents relating to the 22 inherited diseases most frequently tested for in Europe and identified 267 patent claims relating to genetic testing for these conditions.[21] For these 267 claims, 38 percent claimed methods of testing for particular conditions, 25 percent claimed isolated gene molecules, 23 percent claimed primers or probe molecules, and 14 percent claimed genetic test kits.[22]

Analyzing these 267 claims to see whether they could be invented around, the researchers determined that "[n]early half of the claims can be regarded as difficult to circumvent."[23] Claims that are difficult to circumvent, according to the researchers, can only be circumvented after "a substantial investment of money and time, as well as a large amount of inventiveness."[24] Fifteen percent of the claims were considered "impossible to circumvent" or blocking, while the remaining 36 percent were considered easy to circumvent.[25] Thus, 64 percent of the patent claims were either difficult or impossible to circumvent.[26]

The researchers also found that claims to methods of testing for particular sequences were more often blocking or impossible to circumvent than claims to isolated genes.[27] In particular, for those claims directed to isolated gene molecules (25 percent of the 267 patent claims), 3 percent were impossible to circumvent and about half were difficult to circumvent. On the other hand, thirty percent of claims to methods of detecting particular sequences (38 percent of the 267 patent claims) were impossible to circumvent, and a total of 77 percent of these method claims were either difficult or impossible to circumvent.[28]

It should be noted, however, that the authors' terminology differs from that used in this report. The authors' definition of method claims, for example, includes some of the patents this report defines as claims on genes and association patent claims. Despite this difference, the researchers' finding that 64 percent of patent claims are at least difficult to circumvent is consistent with SACGHS' conclusion that patents associated with genetic tests are often difficult, and sometimes impossible, to invent around.

[19] Huys, I., N. Berthels, G. Matthijs, and G. Van Overwalle. (2009). Legal uncertainty in the area of genetic diagnostic testing. *Nature Biotechnology* 27:903-909.
[20] Ibid.
[21] Ibid.
[22] Ibid.
[23] Ibid. P. 906. Subtracting, from 100, the total percentage of patents that were either easy to circumvent or blocking indicates that, when the authors say "nearly half" of the patents were difficult to circumvent, the exact percentage of difficult-to-circumvent patents was 49 percent.
[24] Ibid. P. 905.
[25] Ibid. P. 906.
[26] Ibid.
[27] Ibid. P.906-907.
[28] Ibid. P. 906-907.

Licensing Basics[29]

Patent law does not comprehensively address licensing practices, and the United States Patent and Trademark Office (USPTO) does not regulate licensing practices.

A patent does not allow or compel a patent owner to take any action whatsoever— including using the technology themselves. Rather, it grants the patent holder the right to exclude others from making, using, selling, offering for sale, or importing the invention, for a term of 20 years from the date of filing of a patent application. All patent licenses by their nature constitute an agreement that the patent holder will not exclude the licensee from practicing the claimed invention. Some patent licenses include terms requiring the licensee to practice the invention. Licenses can convey the patent owner's exclusionary right to another party in whole, in part, or not at all. The various types of licenses are discussed in more detail below.

An *exclusive-all-fields-of-use* license conveys the patent owner's exclusionary right to another party in whole. The licensee typically has the right, although usually not the obligation, to enforce the patent rights and the right to sublicense the patent rights to others. Typically, the licensor requires the licensee to use or develop the invention. An *exclusive-by-field-of-use* license conveys the patent owner's exclusionary right to one other party in a well-defined "field." A particular field can be a country, a market area, a technology, or any other mutually agreed upon term. For example, a license could be "exclusive in New Jersey," "exclusive in ophthalmology," "exclusive when the analyte is a nucleic acid," "exclusive when the analyte is a protein," "exclusive for vaccines," or "exclusive for multiplexed tests that analyze 20 or more loci at once." Within the defined field, the patent holder agrees not to grant other licenses, but may grant licenses outside of the defined field. Typically, within the field, the licensee may further sublicense the patent rights. The right to enforce is negotiated on a case-by-case basis. In general, the narrower the scope of the field, the more likely the patent owner is to retain control of enforcement. *Exclusive-by-field-of-use* licenses can also contain a requirement to use or develop the invention within the field or risk losing exclusivity or the entire license.

A *co-exclusive license* restricts the number of additional licenses the patent owner can grant. Unless this license is also restricted by field, the starting assumption is that the license is for all fields. The patent holder can agree to grant no more than one, or two, or any specified finite number of additional licenses. Co-exclusivity can also be combined with field-of-use exclusivity. Generally, the licensee would have sublicensing rights, but probably not the right to enforce without coordination with the patent owner. These licenses also generally contain a requirement to use or develop the invention or risk losing license rights.

A *nonexclusive license* places no restrictions on the number of additional licenses the patent holder can subsequently grant. This license can also be restricted by field, although the starting assumption is that the license is for all fields. Typically, the licensee does not have sublicensing rights, does not have the right to enforce the patent, and there is no requirement to use or develop the invention.

[29] Consultant Lori Pressman contributed much of the content in this section.

Table 1 summarizes these concepts.

Table 1: Key Features of Licensing Types

License Characterization	Number of other licenses which the patent holder can grant	Requirements to use and develop the technology, or the exclusivity terminates, or the license terminates	Rights to enforce the patent against infringers	Rights to sublicense the patent
Exclusive, All Fields of Use	0	Generally Yes	Generally Yes	Generally Yes
Exclusive, By Field of Use	Within the field, 0. Outside the field, unlimited	Generally Yes	Sometimes	Generally Yes, in the Field
Co-Exclusive (no additional restriction on Field)	A defined number: 3, 10, etc…	Generally Yes	Unlikely without coordination with patent holder	Probable
Nonexclusive	Unlimited	Generally No	Generally No	Generally No

Those holding patents protecting genetic tests may use any of the above licensing approaches. When a genetic test would be applicable to different diseases or could be used in multiple contexts (*e.g.*, newborn screening and carrier screening), field of use licenses, either exclusive, co-exclusive, or non-exclusive, may be used.

Licensees often prefer exclusive licenses because they eliminate the risk of competition from other licensees. Exclusivity is seen as especially important when the licensee will be required to make considerable investments of its own to bring the product to market (or to prosecute the patent). On the other hand, a licensor might favor co-exclusive licenses where the market is so large that one licensee alone could not satisfy it or might favor licenses exclusive by field where the invention's market has multiple fields or territories. Where the market is sufficiently large, co-exclusive licenses can in fact increase introduction of a technology because multiple providers leads to competition, and competition lowers prices, improves access, and increases the size of the patent holder's market. Although these considerations can in theory guide licensing decisions, in reality patent holders and prospective licensees have difficulty assessing the particular market conditions their technology will face.[30]

What is given in return to receive a license varies. For example, the licensee may agree to pay a lump sum up front, based on projected benefits. In other cases, the licensee may agree to pay running royalties based on actual sales of the license-associated product or service. The licensee

[30] Heisey, P.W., J.L. King, K.D. Rubenstein, and R. Shoemaker. (2006). "Government Patenting and Technology Transfer." USDA Economic Research Report No. (ERR-15), available at http://www.ers.usda.gov/publications/err15/.

may also grant the licensor access to state-of-the art equipment or related technologies. A combination of payments is also possible. In still other cases, two parties may issue one another cross licenses and collaborate to develop a technology that relies on both their inventions.

As noted in Table 1, in exchange for granting a license, a licensor may also require the licensee to achieve certain milestones in developing the technology, with failure to reach any milestone being grounds for termination of the license; terms in the licensing contract that require the licensee to achieve such milestones are known as diligence conditions or terms. What a patent holder will accept from the licensee in exchange for granting a license can depend on the stage of development of the product. A patent holder who licenses a technology that requires considerable development to a small company usually will not require up-front payments that would hinder the company's development efforts, but will seek later royalty payments and/or a transfer of stock ownership.

I. EFFECTS OF PATENTS AND LICENSES ON PROMOTING THE DEVELOPMENT OF GENETIC TESTS

According to the U.S. Constitution, the purpose of the U.S. patent system is to promote "the progress of science and useful arts . . . ."[31] While the patent system may well fulfill that function overall, the Committee's task was to determine whether there were circumstances associated with genetic research and genetic test development that impaired the ability of the U.S. patent legal system to promote progress in this area or that rendered patents in this area unnecessary. Because patents may promote progress through three different means—by stimulating invention, disclosure, or investment in post-discovery development—this analysis had three sub-parts.

1. Patents as an Incentive for Invention

The idea that patents stimulate inventive activity is based on the premise that without patents, people would not pursue inventions, because any inventions they might create could be copied by others.[32] These copyists, or "free riders," could sell the product just as easily as the original inventor, and such competition would lower the invention's price "to a point where the inventor receives no return on the original investment in research and development."[33] The right of exclusion promised by a patent in effect reassures the would-be inventor or investor that any invention that is created cannot be copied during the patent term. Reassured in this way, the would-be inventor presumably decides to pursue invention, while the would-be investor presumably becomes willing to fund such pursuits, should outside funds be needed.

[31] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974). This utilitarian view of patents "is distinct from moral arguments for patent protection advanced in some European countries . . . ." The drafters of the Constitution did not believe that "inventors have a natural property right in their inventions." Eisenberg, R.S. (1989). Patents and the progress of science: Exclusive rights and experimental use. *University of Chicago Law Review* 56:1017-1086, p. 1025.
[32] Eisenberg, R., op. cit.
[33] Ibid., p. 1025.

Scholars have pointed out, however, that biotechnology researchers have strong incentives to invent that are independent of patents. Academic and industry researchers, who make up the "inventor class" in genetics and biotechnology, often are motivated principally by the desire to advance understanding, help their patients by developing treatments for disease, advance their careers, and enhance their reputations.[34] Scientists'enjoyment of research and solving complex problems also naturally leads to invention.[35]

This understanding of the motivations of scientists is consistent with the findings from the case studies that appear in this report. Scientists interviewed as part of the case studies stated that they would have pursued their research even if their discoveries were not patent-eligible. For example, most of the Alzheimer disease researchers "expressed ambivalence about patenting and none attributed the intensity of the races [to discover Alzheimer disease genes] to patent priority. Rather, they stated that the races were driven by wanting priority of scientific discovery, prestige, scientific credit and the ability to secure funding for additional research based on scientific achievement."[36] Nor did the prospect of a patent encourage the researcher who discovered the Tay-Sachs gene, *HEXA*, or the researchers who discovered the cystic fibrosis gene, *CFTR*.

Box: Genetic Testing for Alzheimer Disease

Alzheimer's disease (AD) as currently classified has several forms, of which two are relevant to genetic testing. A very small percentage of AD cases arise in family clusters with early onset. Familial early-onset AD (EOAD) is usually caused by an autosomal dominant mutation in one of three genes: *PSEN1* (chromosome 14), *PSEN2* (chromosome 1), or *APP* (chromosome 21). A person with one of these fully penetrant mutations will contract the disease if they live long enough, usually developing symptoms before age 60. These families are quite rare, but the 50 percent risk for each child of an affected member to carry the causative mutation means that these tests can be important for those at risk. In contrast to early onset Alzheimer Disease, variants of the *APOE* gene confer increased risk of developing the form of AD most commonly seen in the population. Unlike the risk variants for EOAD, variants in *APOE* that confer increased risk of AD are very common in the general population.

Patents relevant to genetic testing for all four genes have been granted in the United States. The patenting landscape is complex. The *APOE* gene itself is not patented; nor are mutations or polymorphisms of this gene, but testing to predict Alzheimer's risk is the subject of three "methods" patents issued to Duke University and licensed exclusively to Athena Diagnostics. The methods claims are based on *APOE* genotype (both direct and indirect determinations) and "observation" of AD risk. A combination of method and composition of matter claims relating to the *PSEN1* and *PSEN2* genes have been patented and exclusively licensed to Athena Diagnostics. Athena offers genetic testing for *PSEN1*,

[34] Golden, J.M. (2001). Biotechnology, technology policy, and patentability: Natural products and invention in the American system. *Emory Law Journal* 50:101-191. Golden acknowledges, though, that the vast majority of funding for university scientists comes from the Federal Government, which is interested in both advancing knowledge and seeing that inventions reach the public. For the latter goal, government, through the Bayh-Dole Act, encourages patenting and licensing of inventions by funded researchers.

[35] Thursby, J., and M. Thursby. (2007). Knowledge creation and diffusion of public science with intellectual property rights. *Intellectual Property Rights and Technical Change, Frontiers in Economics Series*, Vol. 2, Elsevier Ltd.

[36] Skeehan, K., C. Heaney, R. Cook-Deegan. (2009). Impact of Gene Patents on Access to Genetic Testing for Alzheimer Disease. Appendix A, p. B-14.

PSEN2, *APP*, and *APOE*. Direct-to-consumer (DTC) *APOE* testing has been available through some companies since 2008. Athena Diagnostics has sent several cease-and-desist letters to laboratories offering *APOE* testing. The company charges $475 for *APOE* testing and $1,675-$2,750 for *PSEN1* and/or *PSEN2* testing.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for Tay-Sachs Disease and Canavan Disease

Tay-Sachs and Canavan disease are both neurological autosomal recessive conditions that predominantly but not exclusively affect the Ashkenazi Jewish population. Carrier screening and genetic diagnosis for Tay-Sachs are mainly through enzyme assay, with DNA-based testing for ambiguous cases, or in situations like pre-implantation genetic diagnosis where only a DNA test is possible, or for diagnostic confirmation. DNA-based analysis is the mainstay for both screening and diagnostic confirmation of Canavan disease. Nonprofit research institutions obtained patents on both relevant genes, first the gene that when mutated causes Tay-Sachs (the *HEXA* gene encoding the enzyme hexosaminidase A) and later for Canavan disease (the *ASPA* gene encoding aspartoacylase). The inventor for the *HEXA* patent worked at the National Institutes of Health laboratory and her Tay-Sachs patent was never licensed. That discovery was, therefore, effectively in the public domain, and the genetic test is broadly available. The patents relevant to Canavan disease, in contrast, were licensed by Miami Children's Hospital, which initially enforced its patent rights and planned to issue limited licenses. This decision was highly controversial and led to litigation in which patient advocates were plaintiffs. The lawsuit was about fair access and distribution of benefits, not commercialization per se. The patents were eventually nonexclusively licensed at least 20 times.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for Cystic Fibrosis

Approximately 30,000 Americans have cystic fibrosis (CF). It is the most common severe recessive genetic disorder among Caucasians. The disease is caused by mutations in the *CFTR* gene, which encodes a transmembrane chloride ion channel. One mutation, ΔF508, is responsible for approximately 70 percent of cases (~50 percent of CF patients are homozygous for this mutation) in Caucasian populations. Other mutations are far rarer. Mutation and carrier rates vary by ethnicity.

The University of Michigan, the Hospital for Sick Children in Toronto, and Johns Hopkins University hold patents covering *CFTR* mutations and methods for detecting them. The University of Michigan's patent portfolio includes the important ΔF508 mutation. Currently, at least 63 laboratories in the United States test for the *CFTR* gene. This is possible in part because the three academic institutions that hold patents license them non-exclusively. The initial fee for kit licenses is $25,000, which has not changed in over 15 years. The annual fees too have remained unchanged since the initial license was granted in 1993. The cost of full sequencing tests ranges from $40 to $86 per amplicon (ranging from 29 to 50 amplicons) depending on the laboratory. Mutation testing is also available on several platforms.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Several public commenters also stated that scientists are motivated by concerns apart from patents. The president of a clinical DNA testing laboratory wrote, "DNA patents are not needed as motivation for identification of disease genes. Nearly all disease genes are identified not by private industry, but by researchers working at non-profit institutions. These researchers are

motivated primarily by competition with their peers for faculty positions at top ranked institutions, for publication space in top journals, and for grants. Profit motive from patents plays only a very minor motivational role at best."

Comments on the Draft Report from Sanofi-Aventis U.S., Inc., a pharmaceutical company, echoed these views: "patents do not generally affect research done in this area. We agree that most of this research is done in a university/academic setting. There is a need for academic researchers to perform research and publish their work in order to obtain recognition from their colleagues and to advance their careers."

The Wisconsin Alumni Research Foundation (WARF), the intellectual property management organization for the University of Wisconsin, also agreed in its comments to the Draft Report that most gene discoveries are not patent-driven, pointing out that most gene discoveries arise from basic research and "are not commercially or patent driven but driven by the curiosity of individual scientists whose interest and focus is on exploring disease, health or nutritional states through observations of symptomatic conditions and the desire to trace the origins of those symptoms. Hence, it would be expected that genetic research is not patent driven."

Taken together, this information suggests that scientists are motivated to conduct genetic research by reasons other than patents, suggesting that discoveries will be sought regardless of the availability of intellectual property rights.

Does the Prospect of Patents Stimulate Investment in Genetic Research?

In considering whether patents promote progress by stimulating research and inventive activity, the Committee also weighed the role of patents in stimulating investment to fund such research. Several public commenters discussed the role of patents in stimulating private investment in genetics research. For example, Celera, a manufacturer of diagnostic products, wrote in their submission:

> Even though the Draft Report suggests that scientists who search for gene-disease associations may not be motivated by the prospect of receiving a patent, they cannot conduct this type of research without considerable capital and resources. In our experience, meaningful gene-disease associations are confirmed only if the initial discoveries are followed by large scale replication and validation studies using multiple sample sets, the costs of which are prohibitive for many research groups. Private investors who provide funding for such research invariably look to patents that result from such work as a way of protecting their investment.

The case studies and literature review support these commenters' assertions that patents attract investment to fund genetic research. Both the case studies and literature review reveal that when researchers or companies sought private funds to initiate or advance their genetic research, investors were willing to provide funding because of the prospect of patents being granted as a result of the research. For example, according to a policy paper, Eli Lilly agreed to fund Myriad Genetics' ongoing efforts to find genes associated with breast cancer "in return for licensing

privileges for diagnostic kits and therapeutic products on *BRCA1*." [37] This agreement was based on the assumption that Myriad would in fact be the first to discover the gene and that the company would then patent the gene.[38] The rights promised to Lilly would then be derived from that patent.

Box: Genetic Testing for Breast/Ovarian Cancer and Colon Cancer

Specific mutations in the *BRCA1* and *BRCA2* genes can dramatically increase patients' risks for breast and ovarian cancers. Myriad Genetics, Inc., holds broad U.S. patents on both of these genes and their mutations and is the sole provider of full-sequence *BRCA* testing in the United States. Because Myriad is the only testing service in the U.S. market its practices are a *de facto* standard. Myriad launched testing for the five most common rearrangements (accounting for about a third of all rearrangements) in 2002—and simultaneously began developing testing for all large rearrangements (BART®), which it launched in 2006. Myriad states that it has not enforced patents for services it does not provide (such as paraffin-embedded tissues) and that it has sublicensed *BRCA* testing to three laboratories offering pre-implantation genetic diagnosis. For *BRCA*, Myriad charged $3,120 in 2009, or $38.05 per amplicon (including separate testing for common rearrangements). A 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad on its *BRCA* patents. *BRCA* accounted for two cases of gene patent litigation out of 31 collected gene patent litigation cases, five of which were related to diagnostics. Adoption by third-party payers is becoming more common.

In May 2009, a group of health professional organizations and patients sued the U.S. Patent and Trademark Office, Myriad Genetics, and the University of Utah Research Foundation over Myriad's *BRCA1* and *BRCA2* patents. That case is ongoing in the U.S. District Court for the Southern District of New York and is expected to be appealed regardless of outcome.

Genetic tests for nonpolyposis colorectal cancer (HNPCC) focus on three genes: *MLH1*, *MSH2*, and *MSH6*. Testing for *MLH1* and *MSH2* is protected by claims to an association between the mutated forms of the gene and HNPCC and claims to oligonucleotide probes capable of hybridizing with mutated forms of *MLH1* and *MSH2* (see patent 7,022,472). This patent has not been enforced, and there are multiple providers, both nonprofit and for-profit, including Myriad, for full sequence tests on both genes. Some of these providers test for a third gene—*MSH6*—but whether patents protect testing for this gene is "unclear" according to the case study.

Genetic testing for familial adenomatous polyposis (FAP), another type of colon cancer, focuses on the *APC* gene. Patent 5,352,775 contains claims to the cDNA form of the *APC* gene and probes that are complementary to *APC*. This patent has been non-exclusively licensed, and Myriad and four nonprofits offer full-sequence analysis of the *APC* gene.

Although the patents associated with colon cancer genetic testing are either unenforced or non-exclusively licensed, Myriad charges more per amplicon for its full-sequence tests of HNPCC and FAP than for its full-sequence analysis of BRCA.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

[37] Gold, R.E. and J. Carbone. Myriad Genetics: In the Eye of the Policy Storm. *International Expert Group on Biotechnology, Innovation and Intellectual Property*: September 2008. p. 8.
[38] Berridge, V. and K. Loughlin. (2005). Medicine, the market and the mass media: producing health in the twentieth century. Volume 19 of the Routledge Studies in the Social History of Medicine. p. 267

The prospect of patents also attracted investment in Mercator Genetics, which discovered the hereditary hemochromatosis gene, *HFE*. According to the case study, "The prospects of patents and revenue from diagnostic testing for HH probably stimulated research at Mercator Genetics. However, Dr. Dennis Drayna, co-founder of Mercator Genetics, notes that the company was conceived and initially funded on an agenda much broader than hemochromatosis gene discovery or diagnostic testing alone."[39]

Box: Genetic Testing for Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is an autosomal recessive disorder that results most often from mutations in the *HFE* gene, which regulates iron absorption. Mutations in the *HFE* gene increase the risk for developing symptomatic HH, an iron metabolism disorder that leads to excess iron absorption from the diet, particularly in males. Since the body lacks a natural way to rid itself of the excess iron, in the presence of *HFE* mutations, iron accumulates and can cause organ damage, particularly in the heart, liver, and pancreas. Currently, diagnosis of HH often is based on first-level biochemical tests, followed by second-level genetic testing. Biochemical methods are simple, fast, and inexpensive. Bio-Rad Laboratories, Inc., holds most of the patents relating to the *HFE* gene and HH genetic testing. In 1999, Bio-Rad bought many of those intellectual property rights from Progenitor, which had retained the rights to HH genetic testing following its merger with Mercator, the company that first isolated the *HFE* gene. Mercator scientists first identified the *HFE* gene in 1995–1996, along with two gene mutations, C282Y and H63D, which were present in over 80 percent of people with HH. In 1995 and 1996, Mercator applied for patents related to *HFE* and its mutations. Several patents were granted between 1998 and 2000 and cover the whole *HFE* gene sequence, methods for detecting the C282Y and H63D mutations in the *HFE* gene, and a test kit. Other patents in the same patent family and with the same group of inventors issued between 2000 and 2006 and were assigned to Bio-Rad. These patents included diagnostic methods for a panel of less prevalent mutations. They also covered polypeptides related to the *HFE* gene, and the associated proteins. Some other patents covering additional mutations in *HFE* are not controlled by Bio-Rad, but are far fewer in number. Progenitor's exclusive licensing of patents to SmithKline Beecham Clinical laboratories as a sole source provider of *HFE* testing was controversial. However, since 2000, BioRad has nonexclusively licensed its patents to kit and single-gene test (Analyte-Specific Reagent, or ASR) providers.

Bio-Rad offers two HH ASRs as well, both of which provide for 24 tests at a cost of $2,016, or $84 per test. A purchase of the ASRs comes with a sublicense from Bio-Rad to perform the test. As of May 2007, the GeneTests database listed 37 U.S. laboratories performing targeted mutation analysis for HH. Prices for targeted mutation analysis at 17 of those 37 laboratories ranged from $125 to $467.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Public comments from Axial Biotech, Inc., and Juneau Biosciences, LLC, two companies pursuing the development of genetic diagnostics for, respectively, diseases of the spine and diseases that predominately affect women also indicated that the prospect of patent protection stimulated investment into the companies' initial genetic research.

Patents can attract not only outside investment, but also can motivate established companies to invest their own existing resources in pursuing particular lines of genetic research. For example, the case study concerning colon cancer found that the prospect of patents, most likely on a

[39] Chandrasekharan, S. E. Pitlick, C. Heaney, and R. Cook-Deegan. (2009). Impact of Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis. Appendix A, p. E-3.

therapeutic agent, motivated Human Genome Sciences to conduct genetic research involving sequencing cDNAs encoding receptor proteins.[40] Researchers at John Hopkins who were at the time searching for colon cancer genes decided to partner with Human Genome Sciences to search through the company's database of cDNAs, and the combination Hopkins' research and the information provided by the database resulted in the discovery of the *MLH1* gene involved in colon cancer.[41]

Although these examples show that patents can stimulate private investment into basic gene-disease research, the Federal Government is the major funder of basic research and likely the major funder of basic genetic research.[42] However, definitive data on Federal Government versus private sector investment in basic genetic research are not available.

Public comments also highlighted the role that disease advocacy groups have played in funding of disease-specific genetic research and contributing needed tissue samples. The executive director of an organization focused on the prevention of spinal muscular atrophy (SMA) wrote in a public comment, "In the case of SMA, the patent holder did not even bear the financial burden of the discovery, rather an advocacy group and patients and families suffering from the disease donated funds and tissue samples to a researcher who then patented her discovery and sold it." The chief executive with a non-profit organization focused on improving the treatment and care of individuals with muscular dystrophy, also indicated that an advocacy group had contributed funding for muscular dystrophy genetic research: "The patent on the dystrophin gene [the gene responsible for muscular dystrophy] was awarded to Boston Children's Hospital at the time of the discovery, made by Louis Kunkel, Ph.D., Eric Hoffman, Ph.D., and another researcher in Dr. Kunkel's laboratory. Funding was provided by the Muscular Dystrophy Association as well as private funders."

In sum, the role of patents in stimulating genetic research thus appears to be limited to stimulating private funding that is supplemental to the significant Government funding in this area. Those willing to invest in the research appear to be rarely focused exclusively on diagnostics. In one case, the company hoped the research generated both a diagnostic and a therapeutic, while another company seemed to most likely be interested in only a therapeutic. Moreover, as noted in the conclusion to the prior section, the individual scientists conducting this research are strongly motivated by many factors other than patents. The role of patents in stimulating the investment of capital and resources to develop genetic research discoveries into testing services or test kits is discussed after the following section.

2. Patents as an Incentive for Disclosure of Discoveries

[40] Robert Cook-Deegan, corresponding author for "Impact of Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers," personal communication

[41] Cook-Deegan, R., C. DeRienzo, J. Carbone, S. Chandrasekharan, C. Heaney, and C. Conover. (2009). Impact of patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers to colon cancers. Appendix A, A-27. Angier, N. (1994). Competing research teams find new colon cancer clue. *The New York Times*, March 17, 1994.

[42] The federal government funded 59 percent of basic research in 2006. Science and Engineering Indicators 2008. National Science Foundation, available at http://www.nsf.gov/statistics/seind08/c4/c4h.htm#c4h3.

A second way that patents may promote the progress of useful arts is through the required disclosure of the new invention.[43] In exchange for the patent right of exclusion, an inventor must publicly disclose his or her invention in a manner that enables one of ordinary skill in the inventive field to make the invention.[44] Public disclosure of an invention promotes the progress of useful arts by adding to the public storehouse of knowledge.[45] Furthermore, it is assumed that the disclosure of a new invention will stimulate ideas that lead to the development of other advances.[46]

The concept that patents provide an incentive to disclose is based on the premise that if inventors could not patent their inventions, they would try to maintain them as trade secrets.[47] Such secrecy is undesirable because the public is denied new knowledge.[48] The public also might waste resources duplicating the discovery.[49] The patent system, therefore, can act to ensure that discoveries are revealed and not sequestered.

Although patents are seen as a means of ensuring disclosure, it is doubtful that inventors would keep genetic discoveries secret if they could not patent them. Academic researchers in genetics—as well as academic scientists in general—have strong incentives to publish and present their discoveries, because the norms of science encourage sharing research results, and publication is also necessary to achieve reputational gains.[50] Because prizes, in particular, are based on priority of invention, they stimulate researchers not only to disclose, but to disclose as early as possible. In addition, scientists funded by NIH are expected, under an agency data sharing policy, to share and release in a timely manner "final research data from NIH-supported studies for use by other researchers."[51] (See further discussion later in this report.)

A public comment submitted by The Innovation Partnership, a non-profit intellectual property consultancy, also cast doubt on the idea that patents promote disclosure: "The argument that patents promote progress through the required disclosure of the new invention is not substantiated by empirical evidence. Patent specifications are drafted for the specific purpose of supporting patent claims. They are thus drafted as broadly as possible while disclosing little. Most scientists admit they rarely consult patents to identify useful information. Scientifically relevant disclosures are made in scientific journals."

[43] Eisenberg, R., op. cit.
[44] 35 U.S.C. § 112.
[45] Eisenberg, R., op. cit.
[46] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974).
[47] Eisenberg, R., op. cit.
[48] Ibid.
[49] Ibid.
[50] Fabrizio, K.R., and A. Diminin. (2008). Commercializing the laboratory: Faculty patenting and the open science environment. *Research Policy* 37:914-931; see also Bagley, M.A. (2006). Academic discourse and proprietary rights: Putting patents in their proper place. *Boston College Law Review* 47:217-274. Merton, R.K. (1973). The Sociology of Science.
[51] Final NIH Statement on Sharing Research Data, February 26, 2003

There are also data from the literature suggesting that patents may actually diminish the production of public genetic knowledge. For example, Kenneth G. Huang and Fiona E. Murray have found that "gene patents" negatively affect follow-on public research about those genes.[52] In their study, Huang and Murray looked at gene discoveries that were both published in an academic journal and patented.[53] They then used "publication citations to each gene paper (i.e. peer-reviewed publications citing the focal paper) as a proxy for follow-on [research and] public knowledge accumulation."[54] In particular, they examined the number of forward citations to 1,279 gene papers describing particular human genes with the number of forward citations predicted by a mathematical model of citing trends without patents.[55] After conducting the analysis, Huang and Murray found that the actual number of forward citations was 5 percent less than the number of forward citations predicted by their most stringent model.[56] The results were starker in cases where the genes were strongly linked to human disease; in those cases, the drop in public research was almost 10 percent.[57] These results suggest that gene patents can have a negative impact on follow-on public research, which results in less public knowledge than would occur if the patented genes were only published and not patented.[58]

With regard to the idea that patents are needed to discourage secrecy, Rebecca Eisenberg has pointed out that secrecy is not a viable option for many inventors, because their inventions could be reverse engineered—that is, reproduced without the benefit of the original design plans.[59] In the area of genetics particularly, Randal J. Kirk and others have observed that "trade secret protection is largely impractical for biotechnology and genetic material due to . . . the ease with which these products can be reverse engineered."[60]

In the specific area of genetic tests, test kits could often be easily reverse engineered, while laboratory-developed tests could not be practically maintained as trade secrets. In the case of a test kit, the most common technique necessary for reverse engineering would be ascertainment of the DNA sequences of the nucleic acid components of the test kit—a process that is typically straightforward. A laboratory that uses a laboratory-developed test for its testing service, on the other hand, does not have a physical product that can be obtained and studied for reverse engineering. As such, a testing service provider could offer a test for a genetic disease without revealing the exact gene being tested. As a practical matter, however, the medical community would be unlikely to give such a test much credence without disclosure of the relevant gene, which suggests that laboratory-developed tests could not be practically maintained as trade secrets. Given that trade secret protection does not appear to be a practical option for either test

[52] Huang, K.G., and F.E. Murray. (Forthcoming). Does patent strategy shape the long-run supply of public knowledge? Evidence from human genetics. *Academy of Management Journal*. p. 40.
[53] Ibid., p. 23-24.
[54] Ibid., p.22.
[55] Ibid., p. 26.
[56] Ibid., p. 40.
[57] Ibid., p. 38.
[58] Ibid.
[59] Eisenberg, R.S. (1989). Patents and the progress of science: Exclusive rights and experimental use. *University of Chicago Law Review* 56:1017-1086, p. 1029.
[60] Kirk, R.J., J.L. Hung, S.R. Horner, and J.T. Perez. (2008). Implications of Pharmacogenomics for Drug Development. *Experimental Biology and Medicine* 233: 1484-1497, footnote 8.

kits or laboratory-developed tests, the use of patents to discourage trade secret protection of gene-disease associations seems unnecessary.

In sum, it appears that scientists have sufficient reasons independent of patents to disclose gene-disease associations and that patent claims to genes may be diminishing research that builds on disclosed genetic discoveries.

3. Patents as an Incentive for Investment in Test Development

Legal and economics scholars recognize a third possible mechanism by which patents could promote progress. According to this view, as explained by Wolrad Prinz zu Waldeck und Pyrmont, the patent system "is not so much needed to stimulate inventive activity; rather, it facilitates investment into costly and risky development processes that are necessary to transform a 'mere' invention into a marketable product."[61] Biotechnology industry representatives assert that patents in fact operate in this way, helping small biotechnology companies attract the venture capital needed to further develop promising discoveries.[62] The Bayh-Dole Act is also based on this understanding of how patents operate.[63] The Act was designed to allow and encourage academic institutions to patent inventions arising from Federally supported research and license them to companies on the premise that, absent exclusive rights, companies would not invest resources to develop an invention into a product because free riders could copy the finished product.[64]

Many trade groups and university technology transfer offices that submitted public comments also stated that patents help attract the investment needed for further development of genetic discoveries. For example, the American Intellectual Property Law Association suggested that patents stimulate commercialization and public distribution of inventions.

The Biotechnology Industry Organization, BIO, expressed similar views:

> Patents play a significant role in the investment of capital in the biotechnology markets. Investors measure opportunities in the biopharmaceutical sector through potential sales of the drug/product, the strength of market protection from patents, and other forms of exclusivity (such as orphan drug exclusivity). The patent plays a critical role in helping the innovator take his initial discovery to fruition.

---

[61] W.P. zu W. und P. (2008). Research tool patents after *Integra v. Merck*—Have they reached a safe harbor? *Michigan Telecommunications Technology Law Review* 14:367, p. 372. Under this understanding of the patent system, the incentive provided by a patent operates after a patent has been issued. Conversely, any patent incentives to invent (and to fund inventive activity) and to disclose operate or exist before the patent issues. Eisenberg, R., op. cit.

[62] Ibid. See also *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy: A Report by the Federal Trade Commission*. October 2003, http://www.ftc.gov/os/2003/10/innovationrpt.pdf.

[63] 35 U.S.C. § 201 et seq.; American Bar Association. (2002). The Economics of Innovation : A Survey, http://www.ftc.gov/opp/intellect/0207salabasrvy.pdf.

[64] Ibid.

Commenters with technology transfer and patent licensing experience also discussed the role of patents in test development. For example, WARF contrasted its statement that genetic research is not patent-driven with its view that patents may provide a major incentive for test development because of the protection they afford for the expenditure of risk monies.

In addition to these comments concerning the general idea of whether patents stimulate investment to develop genetic tests, some commenters identified particular tests under development that they said would not be commercialized without the exclusive rights provided by patent protection. The Vice President for Research and Technology Management at Case Western Reserve University stated that a genetic test aimed at detecting early-stage colon cancer is being commercially pursued because the university was able to exclusively license the associated patent rights.

The Director of Licensing at the University of Michigan described a similar situation, stating that an exclusive license to practice a patent protecting a five-gene panel test for lupus erythematosis will motivate the licensee to "invest in both further university research as well as in clinical trials to validate the use of this DNA panel." The director added that because of the exclusive license "[t]he public will become the beneficiary of this testing procedure sooner rather than possibly not at all."

Axial Biotech, Inc., and Juneau Biosciences, LLC, the two companies referenced earlier, also pointed out in their comments that patents had influenced outside investors. Protecting their genetic tests through the patent system has been "a major factor" in persuading investors that their tests could one day be sold at a profit.

On the other hand, the existence of a patent claiming a mutation involved in a rare hereditary disorder may discourage test development. According to public comments from the president of Gene Dx, a company focused on the development of genetic tests for rare hereditary disorders,

> For a rare disorder . . . it may take several years for a laboratory to recover the initial development costs due to the small number of individuals who will be tested. The additional expense associated with negotiating a license of a patent, and paying the up-front and ongoing royalties, can be a strong disincentive to a commercial laboratory in its selection of genetic tests to develop and offer to the community.

The Gene Dx president went on to say that

> [g]ene patents have a severe negative impact on the development, and thus the availability, of genetic testing for rare disorders. . . I can assure the committee that any gene on which there is patent protection falls to the very bottom of my quite extensive list of genetic tests in which my company is interested.

Taken together, this information suggests that patents may stimulate investment in the development of genetic test kits and some laboratory-developed tests, but may discourage investment in the development of tests for rare hereditary disorders.

Are Patents Needed for Test Development?

Thus, while patents may sometimes encourage development of genetic tests and at other times discourage development, it is important to consider a related question, namely are patents needed for test development?

Weighing in on this issue, several commenters suggested that patents are not needed to create laboratory-developed tests because such tests are often developed without patents.[65] According to the American College of Medical Genetics, for example, "genetic tests are typically well-developed and being delivered BEFORE patent holders seek to control the testing. Therefore, it is self-evident that gene patents are not needed to stimulate the development of tests."

The president of a PreventionGenetics, a clinical DNA testing laboratory, made similar points:

> DNA patents are . . . not needed to induce the development of clinical DNA tests. Hundreds of clinical DNA testing laboratories throughout the world are developing thousands of new clinical DNA tests each year. The vast majority of these tests are for genes that are not patent protected. Labs [such as ours] will continue to develop tests at a rapid pace regardless of whether they hold exclusive patent licenses.

The College of American Pathologists also pointed out that unpatented tests have been developed through the work of pathologists in clinical laboratories who have introduced and improved upon the majority of molecular tests largely without patent protection.

Consistent with these comments, the case studies show that laboratories lacking exclusive rights associated with genetic testing for particular conditions have regularly developed genetic tests for those conditions. In particular, patents were not needed to develop genetic tests for hearing

[65] Although they did not refer to tests that have been developed without a patent, law professors Joshua Sarnoff, Jonathan Kahn, and Lori Andrews expressed doubt about the necessity of patents: "Given existing incentives for gene-based science and medical discoveries, there are good reasons to believe that patents are not needed to incentivize DNA-based therapeutic (as well as diagnostic) innovations."

Questions as to the role of patents in stimulating the development of therapeutics were outside the scope of the Committee's study. The Committee notes only that there appears to be a diversity of opinion on this issue. In contrast to the view expressed by these professors, the American College of Medical Genetics wrote in their submission, "In high investment areas such as the development of therapeutics, patents are critical to the long and expensive process of bringing a product to the marketplace." Gold and Carbone have noted that viewpoints on either side of this issue are based on subjective beliefs and that there is no clear empirical evidence to say which position is right: "There are few examples of . . . [therapeutics] being commercialized without intellectual property, but it is unclear whether this is because nobody has tried to do so or whether intellectual property is, in fact, essential to the effort." Gold, R.E. and J. Carbone., op. cit., p. 47-48.

loss, SCA, breast cancer, LQTS, Canavan disease, and HH. Indeed, all of these tests were on the market before the test offered by the relevant patent-rights holder.

Box: Genetic Testing for Hearing Loss

Inherited DNA mutations account for over half of all hearing loss cases. Genetic hearing loss can be classified as "syndromic" or "nonsyndromic," depending on whether there are associated clinical features beyond hearing loss (syndromic) or not (nonsyndromic). Mutations in many different genes have been implicated in genetic hearing loss. In some cases, a single mutated gene is associated with hearing loss (dominant) and in others, symptoms occur when both parental genes an individual inherits are mutated (recessive) or a mutation occurs on the X chromosome (X-linked). Mutations in a few genes are the most commonly tested: *GJB2*/*Connexin 26*, *GJB6*/*Connexin 30*, *SLC26A4*/*PDS*, *MT-RNR1*, and *MT-TS1*. Most hearing loss genes identified to date are not patented. *GJB2* patents have been exclusively licensed, apparently with territory of use restrictions, to the for-profit company Athena Diagnostics for testing in the United States, Canada, and Japan.

The majority of laboratories currently listing the tests are academic health centers. Prices vary for *GJB2* full sequence analysis, ranging from $130-430 per amplicon. Athena charges $472-575 for *GJB2* testing. Genetic tests for *GJB2* and *MT-RNR1*, which are patented, and for *GJB6*, *SLC24A6*, and *MT-TS1*, which are not patented, have been developed and are offered by several providers at similar prices. Several providers have in fact developed test panels that include both the patented *GJB2* and *MT-RNR1* genes as well as the unpatented *GJB6* and *MT-TS1* genes. The acquisition of an exclusive license for *GJB2* diagnostic testing in the United States was presumably integral to Athena Diagnostics' plan to commercialize these tests. While Athena has intermittently enforced its exclusive rights to test for *GJB2* against other service providers, it is not the sole provider of testing. Costs of hearing loss tests do not appear to correlate strongly with patent status. For instance, the price of the most expensive test can be attributed mostly to the costs of sequencing a large gene.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for Spinocerebellar Ataxia

Spinocerebellar ataxia (SCA) is not a single condition, but a group of progressive neurological genetic disorders with common symptoms and disparate genetic causes. SCA is a relatively rare syndrome and many genes are involved. Genetic testing plays a direct role in identifying the molecular defect in some cases. There are currently 15 variants of SCA for which genetic testing is available. Athena Diagnostics holds the patent or has exclusive license to 12 patents that identify mutations in six SCA-associated genes (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *ATXN8OS*) and two other hereditary ataxias (Friedreich's Ataxia and Early Onset Ataxia) included in their Complete Ataxia Panel. Mutations in these genes account for roughly 60 to 80 percent of known SCA cases, depending on the patient's country of origin. Athena was also granted a nonexclusive license by Baylor Medical College for methods for detecting mutations in *ATXN10*, and Athena also does testing for *SPTBN2*, *KCNC3*, *PRKCG*, and *TBP*. Of the 12 patents listed by Athena, half are licensed from the University of Minnesota. Athena Diagnostics has enforced its exclusive licenses and is widely assumed to be the sole licensed laboratory for the above tests. Athena's legal department has sent "cease and desist" letters to some laboratories performing SCA genetic tests for which Athena has exclusive patent rights. SCA genetic tests can be performed individually for as little as $400, for the least expensive single-locus test, or as much as $2,335 for full-sequence analysis of the most expensive full-sequence gene test. The lower-cost tests are for known mutations in the second or subsequent members of a family, once a proband case in that family is characterized. Athena also offers the Complete Ataxia Panel, a compilation of 18 tests that cover the most commonly identified SCA mutations for the price of $7,300. Athena offers a "Patient Protection Program" that caps out-of-pocket payments at 20 percent of the price for cases where Athena directly

bills the patient's insurer.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for Familial long QT syndrome

Familial long QT syndrome (LQTS) affects one in 3,000 newborns. It is a Mendelian condition in which patients' hearts do not recharge appropriately after heartbeats and can lead to life-threatening arrhythmias. Mutations in 12 susceptibility genes account for some 75 percent of familial LQTS; of that 75 percent, mutations in three genes account for most cases. Genetic testing for LQTS is important because knowing which gene (and which part of that gene) is mutated can have a direct bearing on decisions regarding preventive measures and drug treatments. The major LQTS susceptibility genes were discovered at the University of Utah in the mid-1990s. The University of Utah Research Foundation began licensing patents on LQTS susceptibility genes in the late 1990s. Until 2009, at any one time there was never more than a single licensee of the major intellectual property attached to the three genes that predispose to the majority of familial LQTS.

Some Utah patents were initially licensed exclusively to DNA Sciences, which sent out "cease and desist" letters to laboratories offering genetic testing of the genes to which the company had exclusive rights. DNA Sciences also sued GeneDx; GeneDx settled and withdrew from the market. For a period of one to two years, DNA Sciences was not offering testing, but other laboratories that were offering testing withdrew from the market due to its patent enforcement. The exclusive rights to the Utah patents subsequently changed hands twice with corporate mergers and acquisitions, from DNA Sciences to Genaissance and from Genaissance to PGxHealth. From 2005 through 2008, PGxHealth (a Clinical Data subsidiary) was the sole U.S. provider of licensed testing for the five most common long-QT mutations, although it granted international licenses in Australia, New Zealand, and Europe, and a research license to a company in Utah.

The situation changed in 2009 when GeneDx once again began offering LQTS and related gene testing. This market re-entry was enabled by GeneDx acquiring exclusive licenses for some LQTS susceptibility genes held by the University of Utah. In 2008, Bio-Reference Laboratories (BRLI, which owns GeneDx) obtained an exclusive license for several patents giving it rights to test for LQTS type 3, which accounts for approximately 10 to 15 percent of inherited LQTS. BRLI also aggregated IP related to Jervell and Lange-Nielsen syndrome and to LQTS susceptibility genes *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, and *KCNJ2*. Both GeneDx and PGxHealth now offer testing for over ten genes.

PGxHealth's FAMILION® LQTS testing costs $5,400 per index case (a full-sequence test to look for mutations in 11 genes; *KCNQ1* through *SCN5A*; *KCNE1* through *SNTA1*) and $900 per confirmatory test in additional family members (for identified mutations). GeneDx charges $2,500 per index case (mutation screening of ten genes, *KCNQ1* through *SCN4B*) and $350 per confirmatory test.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

When relevant patents were granted, the patent-rights holder enforced their patent rights to narrow or clear the market of these competing tests. For example, the hearing loss case study indicates that there have been intermittent enforcement efforts by the exclusive licensee, Athena Diagnostics, Inc., of patents protecting testing for *GJB2*, with the result that some laboratories have stopped testing. The case study also found that Boston University's Center for Human Genetics stopped offering *GJB2* and *MT-RNR1* testing following Athena's enforcement of

patents protecting those genes. Athena has also enforced its rights with regard to patents protecting SCA testing; the case study on SCA concluded that Athena is now assumed to be the sole provider of SCA testing.

Similarly, Myriad enforced its patents to shut down laboratories that had been offering breast cancer genetic testing since before the patents issued.[66] The case study on LQTS also describes enforcement actions by exclusive licensees that led providers to discontinue testing.

In the case of genetic testing for Canavan disease, the patent holder initially offered infringing laboratories a license to continue performing testing. The case study does not indicate how many laboratories did not accept the license and discontinued testing.

Finally, patent enforcement has also shut down laboratories that were offering HH testing. In particular, Jon F. Merz and his coauthors reported "that many US laboratories began genetic testing for haemochromatosis before the [relevant] patents were awarded, but 30 percent of those in our survey reported discontinuing or not developing genetic testing in the light of the exclusive license granted on the patents covering clinical-testing services."[67]

The development of unpatented tests prior to patent enforcement suggests that developers were driven by considerations other than the promise of a patent and were not dissuaded from test development by the threat of free riders copying their tests. The hearing loss case study suggests that what motivated the laboratories was not profit, but clinical need and demand. That study found that for patented and unpatented genes, demand for testing was the primary factor that determined whether diagnostic testing was offered.

The costs of developing these laboratory-developed tests appear to be relatively modest. According to one group of clinical geneticists, the cost of developing a sequencing-based genetic test is $1,000 per exon.[68] Given that the average gene has 8-10 exons (or coding regions),[69] the cost of developing a laboratory-developed genetic test that relies on gene sequencing as opposed to probe hybridization to detect a single mutation is, on average, between $8,000 and $10,000.

Although the costs of developing a laboratory-developed genetic test are low, a public comment from Celera suggested that the same is not true of test kits. To market a test kit, the developer must obtain approval of the kit as a medical device under the Food, Drug, and Cosmetic Act, a process that, according to Celera, involves considerable cost:[70]

[66] William-Jones, B. (2002). History of a gene patent: tracing the development and application of commercial BRCA testing. *Health Law Journal* 10: 123-146.
[67] Merz, J., A.G. Kriss, D.G.B. Leonard, and M.K. Cho. (2002). Diagnostic testing fails the test: the pitfalls of patents are illustrated by the case of haemochromatosis. *Nature* 415:577-579.
[68] Das, S., S.J. Bale, and D.H. Ledbetter. (2008). Molecular genetic testing for ultra-rare diseases: models for translation from the research laboratory to the CLIA-certified diagnostic laboratory. *Genetics in Medicine* 10:332-336, P. 336.
[69] Sakharkar, M.K., V.T. Chow, P. Kangueane. (2004). Distribution of exons and introns in the human genome. *In Silico Biology* 4: 387-393.
[70] 21 U.S.C. § 321(h); 21 C.F.R. Part 809.

> A product manufacturer must design, validate, and manufacture each diagnostic product in compliance with FDA's Quality System Regulation, which includes good manufacturing practices and design control requirements that are costly to implement. In addition, diagnostic products submitted for FDA registration must be accompanied by data from clinical trials which are also costly undertakings. Thus, patent protection is a necessary incentive to investors in mitigating their risk in funding companies that engage in research and development of genetic tests [marketed as test kits].

This claim—that the cost of developing a test kit are so high that patent protection is needed to fund test kit development—was one the Committee had heard from other parties and examined. Two case studies contain facts relevant to whether the patent incentive is needed for test kit development. First, the case study on Tay Sachs indicates that a company expressed interest in developing a test kit for genetic testing in Tay Sachs, but would do so only if the gene was patented. However, when the gene was patented, the patent holder—the National Institutes of Health (NIH)—decided not to enforce it or license it; no test kit has been developed to date, although laboratory-developed tests are in use and testing is broadly available. While the one company described in the case study indicated that the patent was necessary for it to pursue test kit development, it is not clear why other companies have not pursued development of a test kit. Whether other companies are discouraged by the lack of an exclusive license or some factor unrelated to patents, such as their perception of low demand for the test, is unknown.

The second relevant case study in this area—the case study on genetic testing for CF—suggests that exclusive rights are not necessary for the development of a test kit for a common genetic condition. Specifically, the CF case study shows that multiple parties have obtained a non-exclusive license to develop a test kit for CF testing. At the time of the case study's writing, two licensees had obtained FDA approval for their test kits, and other companies were in the process of seeking FDA approval of their test kits.[71] The fact that these licensees will have to compete against one another has not dissuaded any of them from pursuing test kit development. The case study indicates that 63 American laboratories perform CF Testing: "The majority of those labs are academic medical centers or hospital-based genetic testing laboratories that use CF test kits developed under these licenses."[72]

Thus, based on this information, patent-derived exclusive rights are neither necessary nor sufficient conditions for the development of genetic test kits and testing services. In the area of genetic testing services particularly, where development costs are not substantial, patents were not necessary for the development of several genetic tests. This conclusion is revisited in the recommendations section of this report, where the necessity of patents is examined in light of a potential changes in the regulatory oversight of genetic tests.

II. OTHER POSSIBLE BENEFITS OF PATENTS AND LICENSES

[71] Robert Cook-Deegan, one of the authors for "Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis," personal communication

[72] Chandrasekharan, S., C. Heaney, T. James, C. Conover, and R. Cook-Deegan. (2009). Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis. Appendix A, C-7.

Public comments and the case studies make reference to other possible benefits of patents associated with genetic tests. The breast cancer case study, for example, suggests that exclusive rights holders have significant incentives to educate physicians and patients and that such patent-driven educational efforts can have the benefit of increasing awareness of the test. However, there are concerns that in addition to benefits, marketing (promotion) of tests may lead to overutilization, inappropriate testing and patient harm. In response to these concerns, Myriad has stated, according to the case study, that it is not trying to expand testing to inappropriate patients, but merely to saturate testing among high-risk families.

Nevertheless, greater federal regulation of advertising claims made about laboratory-developed tests would provide further assurance that companies that advertise these tests do not make inappropriate claims. A separate paper under development by the Committee on direct-to-consumer genetic testing will address how the Federal Government can improve regulation of advertising claims made by providers of laboratory-developed tests.

Another possible benefit of patents the Committee considered was whether patents provide an important incentive to pursue insurance coverage for a test. BIO, for example, stated during a public comment session at the October 2009 SACGHS meeting that patents in this area have this benefit. The case study on breast cancer, however, suggests that both sole providers and non-exclusive providers have an equal incentive to obtain coverage: "[c]ompanies offering genetic testing have incentives to negotiate the complex coverage and reimbursement landscape on behalf of patients using their services."[73] Furthermore, having multiple providers pursuing coverage should lead to greater cumulative coverage than the coverage obtained by one provider, particularly if that provider has decided not to accept particular insurers or insurance programs.

The Committee also considered whether patents associated with genetic tests have the benefit of ensuring that genetic testing is limited to patients for whom it is clinically useful. That is, because a patent-derived license can be used to limit the use of patent rights to only those situations where testing is clinically useful, can the use of licenses in this way be counted as benefit of patents? An example of using a license to enforce clinical guidelines is described in the Alzheimer disease case study. According to that case study, the discoverer of the patented *APOE* gene stated that a clause was added to the exclusive license requiring the test to be used only in patients with confirmed dementia.

Notwithstanding the clause's possible salutary effect in this case, there is no guarantee that other holders of patents protecting genetic tests will adopt this approach to licensing. Patent law does not require the holders of genetic-testing-related patents to devise licenses that enforce clinical guidelines. As such, the use of patents to enforce clinical guidelines cannot be viewed as a system-wide benefit of patents protecting genetic tests. Moreover, given the evolving evidence base on the clinical validity and utility of genetic tests, licensing provisions outlining clinical guidelines may quickly become outdated. For example, recent data now suggest that *APOE* testing for Alzheimer disease risk prediction might indeed be desirable in a number of clinical

[73] Add citation to case study.

situations, contrary to the assumed stipulations of the license.[74] Thus, there may be more effective ways of enforcing clinical guidelines than through terms of a patent-derived license.

III. THE EFFECT OF PATENTS AND LICENSING PRACTICES ON CLINICAL AND PATIENT ACCESS TO GENETIC TESTS

As the Introduction to this report suggests, the patent system involves a trade-off between the potential benefits of patents and the potential social harms that can result from rewarding a patent holder exclusive rights.[75] Having evaluated one side of this trade-off in Sections I and II—specifically, the benefits of patents associated with genetic tests—Sections III, IV, and V examine whether such patents are causing social harms by creating barriers to clinical and patient access, test quality, and the development of new testing innovations.

Patents and Licensing Practices and the Price of Genetic Tests

One way patents associated with genetic tests might limit clinical or patient access is by raising prices above what would exist in a competitive market. Although the case studies attempted to evaluate how patents and licensing practices affect the price of genetic tests, some case studies did not yield definite conclusions because of difficulties in obtaining relevant data and challenges in determining the relative contribution of various factors, including overhead costs, to price.

One of the case studies where there was a definite conclusion was the one concerning breast and colon cancer testing, where it was found that the per-unit price of the full-sequence *BRCA* test, which often is cited as being priced very high, was actually quite comparable to the price of full-sequence tests done on colon cancer, for which associated patents are non-exclusively licensed. On the other hand, the case study on LQTS suggests that the price of the patent-protected test was higher than it would have been had the test been unpatented, with the potential that this premium is reducing patient utilization of the test. In that case study, the authors write, "[W]e believe that a competitive presence could have accelerated the test to market and lowered the cost from its current $5400."[76]

In addition, it appears that the test developers of the Canavan disease genetic test used their patent monopoly to establish restrictive license conditions and sought license fees that exceeded what laboratories offering similar tests for Tay-Sachs disease were willing to pay. A consortium of the Canavan Foundation, the National Tay-Sachs and Allied Diseases Association (NTSAD), the National Foundation for Jewish Genetic Diseases, and the Canavan Research Fund organized against the patent holder, initiated a lawsuit roughly a year after the license terms were first proposed, and negotiated a sealed and confidential settlement that altered the license terms in a

[74] Green, R.C., et. al. (2009). Disclosure of APOE genotype for risk of Alzheimer's disease. *New England Journal of Medicine* 361:245-254.
[75] Mazzoleni, R. and R.P. Nelson. (1998). The benefits and costs of strong patent protection: a contribution to the current debate. *Research Policy* 27: 273-284.
[76] Angrist, M., S. Chandrasekharan, C. Heaney, and R. Cook-Deegan. (2009). Impact of Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome. Appendix A, F-4.

way that the plaintiffs apparently considered acceptable. Even after the settlement, however, there was an average price difference between genetic tests for Canavan disease and tests for Tay-Sachs disease. The case study concludes that "The average price per amplicon for Tay-Sachs . . . is $111.50 while the price per amplicon for Canavan disease is $199.58: a significant difference that could reflect a patent premium."[77]

In addition to these findings from the case studies, a number of commenters claimed that patents affect the price of genetic tests, but they did not provide concrete evidence of such patent price effects. Nor did any articles reveal evidence of exclusive rights resulting in an inflated price for a genetic test.

In sum, although the case studies identified patents and exclusive licenses that appear to be causing high-prices for some genetic tests, no evidence was found that patents and exclusive licenses have consistently led to higher prices for genetic tests.

Clinical Access to Existing Genetic Tests

Based on its review of the literature, case studies, and public comments, the Committee found that the patenting and licensing of genetic tests has limited the ability of clinical laboratories to offer genetic testing. This limitation, in turn, can affect patient access, the quality of testing, and efforts to innovate. The effect of patents and licensing practices on the quality of genetic tests and innovations in testing are discussed in greater detail in later sections. Committee findings in support of the conclusion that patents and licensing practices have affected the ability of clinical laboratories to offer genetic tests are presented below.

In 2002, Merz and his coauthors reported that approximately 30 percent of laboratories discontinued or did not offer the test for HH, in light of the exclusive license for the test given to and enforced by SmithKline Beecham Clinical Laboratories. [78] Among these 36 laboratories, 22 of them stated that patents were the reason they had stopped, while 10 reported that patents were one of several reasons why they discontinued or not developed a test.[79] Merz and his coauthors concluded that the narrowing of the market had implications for test quality and patient access, because there was little opportunity for validation and confirmation studies and limited ability to incrementally innovate or develop clinical expertise.[80]

With regard to patient access, however, the HH case study found that any initial problems were solved through a later broadening of licensing practices:

> In 2007 and 2008, compared to 2002, we found little controversy surrounding *HFE* genetic testing and the licensing model has evolved to include several

[77] Colaianni, A., S. Chandrasekharan, and R. Cook-Deegan. (2009).Impact of Patents and Licensing Practices on Access to Genetic Testing and Carrier Screening for Tay-Sachs and Canavan Disease. Appendix, H-11.
[78] Merz, J., Kriss, A., Leonard, D., and M. Cho. (2002). Diagnostic testing fails the test: The pitfalls of patents are illustrated by the case of haemochromatosis. *Nature* 415:577.
[79] Ibid.
[80] Ibid.

> providers and sublicensing for use on different platform technologies. The past licensing practices of SmithKline Beecham Clinical Laboratories (SBCL) (exclusive licensing model) were controversial, but the current owner of patent rights, Bio-Rad, Ltd., appears to have a broad sub-licensing model that has resulted in broader clinical and patient access and less public conflict.[81]

Researchers followed up on the 2002 study with a more comprehensive survey of the effect of patents and licensing practices on laboratories' performance of genetic tests. Specifically, in 2003, Mildred Cho and her coauthors surveyed directors of laboratories conducting clinical genetic testing, making the following key findings:

> Twenty-five percent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported deciding not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories. We found 22 patents that were relevant to the performance of these 12 tests. Fifteen of the 22 patents (68%) are held by universities or research institutes, and 13 of the 22 patents (59%) were based on research funded by the United States Government.[82]

The survey found little support for the value of patenting among laboratory directors, and the authors concluded that "patents and licenses have a significant negative effect on the ability of clinical laboratories to continue to perform already-developed genetic tests" and continued by stating that "we do not know whether patients who were denied access to these tests had testing performed by another laboratory . . . ."[83]

The case studies found other instances of exclusive rights being enforced to prevent other clinical laboratories from offering testing:

- The exclusive rights Myriad Genetics holds on the *BRCA* genes has been used to stop other laboratories from conducting breast cancer genetic testing;
- Athena Diagnostics has intermittently used its exclusive rights to various hearing loss genes to stop some laboratories from testing;
- Athena has also enforced patents associated with Alzheimer disease testing to reduce alternative providers;
- DNA Sciences used its exclusive rights to LQTS genes to attempt to clear the market; and
- Miami Children's Hospital enforced its patent on the Canavan disease gene resulting in laboratories stopping testing or paying a royalty fee to continue performing testing.

The case study on SCA genetic testing also provides a lengthy discussion of the effect on clinical

[81] Chandrasekharan, S., E. Pitlick, C. Heaney, and R. Cook-Deegan. (2009). Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis. Appendix A, p. E-2
[82] Cho, M.K., et al. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnosis* 5(1):3-8., p. 3.
[83] Ibid., p. 8.

access of Athena Diagnostics' enforcement of patents covering SCA genes:

> Athena's legal department has sent "cease and desist" letters to some laboratories performing SCA genetic tests for which Athena has exclusive patent rights. In another instance, the Diagnostic Molecular Pathology Laboratory at the University of California Los Angeles stopped offering testing for SCA over two years ago, after receiving a "cease and desist" letter from Athena Diagnostics. According to Dr. Wayne Grody, Director of the Laboratory, the terms of the sublicense offered by Athena Diagnostics were not economically viable for the laboratory. Attempts to negotiate terms of a sublicense have not been successful to date. It is unclear to what extent cessation of testing at UCLA has affected patient access to SCA testing. Dr. Grody indicated that samples are now sent to Athena Diagnostics for clinical testing. Several other laboratories are also listed on GeneTests.org for adult SCA diagnoses. Comprehensive Genetics Services offers a complete panel of SCA tests but did not respond to questions about patents or licensing in phone interviews. We recently became aware that Boston University reached a settlement with Athena Diagnostics regarding testing for SCA and several other conditions and no longer offers SCA testing.[84]

Several public commenters also provided information relating to clinical access. Two public comments stated that clinical laboratories offering multiplex testing do not report medically relevant results relating to patent-protected genes included in the array for fear of liability. For example, the technical director of a medical laboratory wrote,

> Multiplex assays are being used clinically at least in the constitutional area for individuals with birth defects and/or developmental issues and autism; areas of arrays where patented genes lie must be identified and masked, so that if a patient has a copy change (deletion or duplication) present, the information cannot be reported by the lab performing the test unless they have paid license fees (if even available) for the gene(s). This is expensive to labs to spend resources keeping up with which genes are patented and which are not and which genes are licensed and which are not and how, and altering work-flow so as to not report data regarding certain sequences—this cost will be passed on to the patient and the insurers. This also has the potential for patients to remain undiagnosed for certain conditions, if someone has an alteration that cannot be reported by a particular testing lab, even after having spent large sums of money for their diagnostic testing.[85]

Another public comment stated that the exclusive licensee of a patent covering the detection of the leukemia-associated *FLT3* gene has stopped several laboratories, including the Mayo Clinic,

[84] Powell, A., S. Chandrasekharan, and R. Cook-Deegan. (2009). Spinocerebellar ataxis: patient and health professional perspectives on whether and how patents affect access to clinical genetic testing. Appendix, G-6.

[85] While it may be that not reporting test results prevents the patent holder from becoming aware of the use of patent-protected genes or probe molecules, performance of the test is still infringement so long as the probe molecules used in the test are claimed by the patent or equivalent to what the patent claims.

from performing such testing. The commenter, the medical director of molecular oncology at a blood center, stated that physicians have complained of a slow turnaround time in receiving testing results from the exclusive licensee. The commenter added, "If true, this delay in receiving test results could have a negative impact on patient management."

In sum, some patents associated with genetic tests and exclusive licensing practices have limited clinical access to genetic tests. Some patent holders have used their property rights to prevent other laboratories from offering testing, thereby becoming in some cases the sole provider of the test. Non-exclusive licenses can also limit clinical access if laboratories cannot afford or are unwilling to pay the royalty fees associated with the non-exclusive license. It is important to note, however, that limitations in clinical access do not necessarily limit patient access. For instance, the nonexclusive licensing fees providers have to pay to offer HH testing do not appear to be affecting patient access to the test.

Patient Access to Existing Genetic Tests

The case studies generally found that for patented tests that were broadly licensed there was no evidence of patient access problems. However, in those cases where an exclusive-rights holder narrowed or cleared the market of competing tests through patent enforcement, some problems did occur. For example, in the case of testing for LQTS, two successive exclusive licensees enforced their patent rights from 2002 to 2004 even though they were not yet offering a commercial test. This resulted in a period of 18 months when testing was only available from academic research laboratories and not from clinical laboratories certified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[86] While acknowledging that the evidence is incomplete, the case study concludes that some patients during this period (2002-2004) may have been prevented from receiving testing for this potentially lethal disorder. The case study describes the effect as "small but tangible" and suggests that "this negative effect would likely have been larger had there been greater awareness, understanding and acceptance of genetic testing on the part of cardiologists and electrophysiologists at that time."[87]

Enforcement of patent rights has also created access problems when the exclusive-rights holder does not accept a particular insurance, including Medicaid or Medicare. Patients who are covered by these payers must either forgo a needed test or pay out of pocket for it. For example, Athena Diagnostics, which has exclusive rights to patents related to the hearing loss gene *GJB2*, has

[86] The Clinical Laboratory Improvement Amendments of 1988 require certification of clinical laboratories that perform laboratory examination of materials derived from the human body. 42 U.S.C. § 263a. As explained in the Committee's report on the oversight of genetic testing, "Genetic testing laboratories must undergo inspections (also called surveys) every 2 years to assess their compliance with CLIA quality requirements such as personnel qualifications and responsibilities, quality control (QC) standards, PT [proficiency testing], QA [quality assurance, and record keeping." SACGHS. (2008). U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services.

[87] Angrist, M., S. Chandrasekharan, C. Heaney, and R. Cook-Deegan. (2009). Impact of Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome. Appendix, F-1.

enforced its rights to narrow the market of other tests.[88] Because Athena does not accept MediCal, the California Medicaid program, access for MediCal patients may have suffered as a result.

Athena, which is also the sole provider of SCA testing and *APOE* and *PSEN2* testing relating to Alzheimer disease, is not a participating provider in any Medicaid program.[89] Medicaid patients, however, can apply for a discount of up to 80% through Athena's Financial Assistance Program.[90] To request this discount, a Medicaid patient must submit payment, a completed Financial Assistance Program Application, proof of Medicaid eligibility, proof of household income with tax documentation and documentation of total medical bills in the last 12 months.[91] Knowledgeable clinicians, including SACGHS members, have not observed wide uptake of this program by patients and regularly see patients simply forgoing testing. Clinicians may be observing low participation in Athena's program because even with the 80% discount, the costs of some tests are so high—in the range of $10,000—that patients would still have to pay a considerable amount.

Clinicians who submitted public comments on the draft form of this report have also observed access problems when an exclusive rights holder does not accept a particular insurance, but enforces its patents to narrow or clear the market. For example, two genetic counselors from Emory University wrote in their public comment,

> Unfortunately, there are also labs [that are exclusive licensees or patent holders] that choose not to contract with Medicaid or Medicare at all. The end result is that access to a genetic test can be largely influenced by a patient's socioeconomic status and geographical location. Given the fact that approximately 50% of Georgia births are covered by Medicaid, this represents a major problem in our state.

A recently filed legal complaint challenging the *BRCA* patents held by Myriad Genetics also alleges access problems resulting from Myriad's decision not to accept particular insurers. According to that complaint, one plaintiff covered by MediCal and another plaintiff covered by MassHealth, the Massachusetts Medicaid program, cannot afford to pay for the full cost of *BRCA1*/*BRCA2* testing out-of-pocket and have had to forego recommended testing because Myriad did not accept their insurance, even though MassHealth would cover *BRCA* genetic testing.[92] Although Myriad, according to the case study, has reduced "the number of self-pay patients to single-digit percentages of its clientele[,]"[93] allegations such as these suggest that

[88] The case study indicates that even though Athena has enforced its patent right, it does not appear to have completely cleared the market of competing tests.
[89] Athena Diagnostics web site. Ordering & Billing section. http://www.athenadiagnostics.com/content/ordering/
[90] Ibid.
[91] Ibid. See in particular the linked Financial Assistance Program Application.
[92] Association for Molecular Pathology Compl. ¶¶ 21, 24, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf
[93] Cook-Deegan, R., C. DeRienzo, J. Carbone, S. Chandrasekharan, C. Heaney, and C. Conover. (2009). Impact of Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing

patient access problems are occurring.

While an exclusive rights holder's refusal to accept a particular insurance can cause access problems for some patients, an exclusive rights holder's clearance of the market denies all patients of the ability to access a confirmatory genetic test from a different laboratory. The ability to obtain a confirmatory test from a second laboratory is important because genetic test results can have implications for major medical decisions, such as whether to have a mastectomy or surgical removal of the ovaries. Confirmatory testing by another lab is the laboratory equivalent to the time-honored practice of obtaining a second opinion from a clinician. The legal complaint filed against Myriad names one plaintiff who would have liked a second opinion on her *BRCA1/BRCA2* genetic test results, but has instead had to make major medical decisions based on the Myriad test results alone.[94]

Other types of access problems can arise when a patent rights holder has cleared the market of other laboratories that were offering the genetic test provided by the patent rights holder. For example, patients who want to test their fetuses for particular conditions may not be able to if the sole provider refuses to conduct its test on fetal samples, as is the policy of the sole provider of LQTS testing. Although it is not clear whether there are patients who want prenatal testing for LQTS, such testing was at one time offered but subsequently shut down through patent enforcement. The availability of—and therefore access to—carrier or newborn screening for particular conditions could also be prevented if a rights holder has cleared the market but lacks the ability—or the willingness—to screen all carrier or newborns. This concern was raised by the Association for Molecular Pathology. In particular, the Association was concerned that the exclusive licensee of patents relating to SMA testing, Athena, and its sublicense would be unable to handle the volume of testing that would be generated from carrier screening for SMA.

In sum, the Committee found that access to genetic tests for significant segments of the population—especially indigent patients—has been impeded when a patent rights holder does not accept all insurers or insurance programs and uses its patent rights to prevent other laboratories from offering the test. Patients covered by the unaccepted insurers or insurance programs cannot afford testing and choose to forgo it. If other laboratories could offer the genetic tests in question, these patients would have a greater chance of obtaining access because it would be likely that at least one of the other laboratories would accept their particular insurance.

Access to confirmatory testing is completely impeded when a patent-enabled sole provider exists. That is, patients who desire a confirmatory test from a second laboratory are unable to obtain this second-opinion test in those cases where the patents right holder has cleared the market of other laboratories offering the test.

Other access problems may have occurred or may be occurring. In particular, the lack of availability of LQTS testing during an 18-month period due to patent enforcement would have

---

Breast and Ovarian Cancers to Colon Cancers. Appendix, A-31. The case study indicates that Myriad has established contracts—or accepts—over 300 insurance carriers.

[94] ACLU Compl. ¶ 23, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf.

caused access problems if there were patients seeking the test at that time. Whether there were such patients is not documented. Now that LQTS testing is available, access to testing of fetal samples may be suffering because the sole provider will not perform the test on fetal samples. Here again, however, it is unclear whether there are any patients who desire prenatal testing.

Finally, another lesson that was drawn from the Committee's study—specifically the case study on Canavan disease testing—is that controversies concerning patient access to patent-protected genetic tests are more likely to occur when the interests of medical practitioners and patients are not taken into consideration during the process of licensing the relevant patents.

Are Patient Access Problems Better Addressed through Health Insurance Reform?

Discussion by both the patents task force and the Committee at its October 2009 meeting raised the issue of whether the patient access problems described here were better addressed through changes in health insurance law and policy rather than changes in patent law and policy. A public comment submitted by Celera on the public consultation draft form of this report made a similar point: "issues related to clinical and patient access . . . may be better addressed through . . . coverage and reimbursement systems for such services."

However, it is not clear how legal changes affecting the practices and policies of health insurers could solve these patient access problems because these problems are caused not by any behavior by health insurers, but by an exclusive rights holder's decisions. It is the decision of a rights-holding sole provider not to accept particular health insurance that has caused access problems for some patients, just as it is the decision by an exclusive rights holder not to permit other laboratories to offer testing that has prevented second-opinion testing. Likewise, it is the decision by the company offering LQTS testing not to offer prenatal testing that may be denying access to prenatal testing.

Insurance law changes also would not eliminate the barrier patents present to the development of new testing innovations, a situation described in section IV. Nor would health insurance reforms address the problems that patents can cause in the quality of genetic tests. Neither of these problems is caused by health insurer's policies or practices.

IV. THE EFFECTS OF PATENTS AND LICENSING PRACTICES ON THE QUALITY OF GENETIC TESTS

The breast cancer and LQTS case studies documented concerns about the quality of tests provided by sole providers. The breast cancer case study cites a commentary in the *Journal of the American Medical Association* (*JAMA*) and testimony before Congress about the test's inability to detect genomic rearrangements, insertions, and deletions. While Myriad Genetics was already working on addressing these deficiencies, the case study suggests that the *JAMA* article may have accelerated Myriad's efforts. The LQTS case study suggests that more competition might have brought about greater progress in understanding the complicated genetics of the disease, which in turn would improve testing for the disease.

A public commenter, a medical doctor, also stated that greater competition for certain genetic tests would improve their quality:

> In all aspects of my medical practice aside from genetic testing, if a consultant or laboratory fails to provide adequate service, doesn't provide optimal interpretation of results, makes routine errors, or has unwieldy paperwork requirements, I have options to seek out a different laboratory or consultant to optimize care for my patients. In the area of genetic testing for neurologic disorders, I often have no such options. One laboratory has exclusive rights to diagnostic testing. There is no oversight group that is capable of insuring quality care. The marketplace can, however, drive quality. In speaking with my colleagues at national meetings about this issue, it is clear that our experiences regarding quality are highly congruent. However, each individual has only a few problems per year, and limited time to try to interest any oversight organization in addressing them. If we had a choice of labs for genetic tests, a marketplace message would quickly be sent and patient care overall would be improved.

Another medical doctor who submitted a comment expressed similar views about the advantages of competition in testing:

> The greater the number of laboratories performing such analyses, the better the possibilities for advances in assay performance. This is true even if all available tests are of high quality and subject to excellent quality control procedures.

The existence of multiple laboratories offering the same test can facilitate confirmatory testing in the clinical context, which is perhaps the best way of allaying concerns about the quality or accuracy of a particular provider's test. When samples cannot be sent to another, independent laboratory to confirm a diagnosis, concerns about quality—whether justified or not—seem more likely to arise. A public comment revealed that such concerns have arisen in the case of genetic testing for the dystrophin gene, which is exclusively provided by Athena. In the comment, the chief executive of an organization focused on improving the treatment and care of individuals with muscular dystrophy explained the context within which concerns have been raised:

> [C]linical trials are in process and in development targeted to specific mutations within the dystrophin gene. Because these strategies are targeted to specific subsets of patients, genetic testing becomes a critical factor in terms of screening patients, participation in trial, and ultimately an approved therapy for . . . [muscular dystrophy]. This makes the quality of testing an extremely important issue for our families. We have been contacted by several families with concerns about the accuracy of their test results. We have also been contacted by clinicians with concerns about test results and the lack of laboratories to provide confirmatory testing and to evaluate cases where a mutation is not detected by Athena.

While this comment should not be taken as evidence of actual quality problems in Athena's test, it suggests that an effective way to address concerns about laboratory quality or test accuracy would be to ensure independent confirmatory testing. Moreover, the only way to assess whether concerns about quality are founded or not would be through such independent testing.

In contrast to the view that having multiple providers is the best way to ensure test quality, a medical professional society concerned with clinical laboratory science submitted a comment stating that CLIA should remain the primary vehicle for ensuring the quality of testing. A manufacturer of diagnostic products in its comments also favored existing oversight systems as the best means of addressing test quality: "quality may be better addressed through the evaluation of the regulation and oversight of genetic tests . . . ."

While these commenters suggest that testing quality depends on regulatory oversight, Kathleen Liddell and her coauthors have suggested that quality depends on the number of providers—and that having fewer providers may be preferable to having many. In particular, Liddell and her coauthors argue that

> there are certain technical advantages of centralising the provision of genetic tests with a small number of laboratories. It is far easier to ensure a consistent quality of testing across one or two labs, than to produce a standardised kit suited to wide deployment. This is particularly so for complex tests, which may be difficult to turn into a standardised kit which can be used in multiple labs, and which may best be carried out by major reference laboratories until consistent sampling procedures are established. One respondent [in the authors' survey] also pointed out that monopoly provision of genetic services does not run wholly against the grain. The "reference lab" model is well accepted as a way of improving the quality of rare disease genetic tests.[95]

Despite this suggestion that quality is best addressed by limiting the number of providers of a genetic test and other suggestions that quality is best addressed through regulatory oversight, the Committee concluded that the ability to independently verify test results and the use of proficiency testing which entails multiple labs scrutinizing the same sample is the best means to ensure the quality of genetic tests. This conclusion is echoed by laboratory directors and is consistent with standard mechanisms currently used to ensure test quality. Robust proficiency testing programs, which exist throughout the country, depend on multiple laboratories, and the possibility of confirmatory testing of diagnostic results is prevented in the setting of a sole-source provider. Thus, concerns about the quality of genetic tests are more likely to arise when only a single provider exists. The Committee was also persuaded that competition among labs is a potent mechanism for ensuring quality as it provides clinicians with alternatives and thus harnesses market forces for continued quality improvement.

[95] Liddell, K., Hogarth, S., Melzer, D., and R.L. Zimmern. (2008). Patents as incentives for translational and evaluative research: The case of genetic tests and their improved clinical performance. *Intellectual Property Quarterly* 3:286-327. p. 293.

Finally, there have been calls (e.g., by the NRC Committee in their report *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*) for a provision to allow verification or second opinion testing when a sole provider exists.[96] While not disagreeing with the spirit of the NRC recommendation, the Committee does not think that such a narrow provision would produce the intended effect because there would be little incentive, and many disincentives, for a laboratory to develop and maintain a test simply to provide second opinions or verification requests. Moreover, the volume of such requests could be insufficient to ensure optimal test quality.

V. THE POTENTIAL EFFECT OF PATENTS AND LICENSING PRACTICES ON GENETIC TESTING INNOVATIONS

In examining the effects of patents and licensing practices on genetic tests, the Committee has been concerned not only with existing effects, but also with the potential impact of patents and licensing on future innovations in testing. A recent innovation in genetic testing is multiplex testing, which involves simultaneously testing multiple genetic markers. This efficient form of testing could be used in various contexts, including in newborn screening. It is anticipated that such screening might eventually be done by affordable whole genome sequencing—an innovation that is likely to develop in the coming years.[97] These innovations and others—and the challenges to their development and use posed by patents and licensing practices—are discussed below.

The Potential Effect of Patents and Licensing Practices on the Development of Multiplex Tests

Several technologies have been developed for simultaneously testing multiple genetic markers (either genes or sequences of phenotypic relevance outside of genes) with a single test. Such multiplex testing can be useful when a condition involves multiple genetic factors or when one wants to simultaneously test multiple conditions that have one or more potential genetic causes. In the past, when multiple genetic markers had to be tested, each genetic marker would be tested in a separate test, making testing complex, time-consuming, and expensive. As such, multiplex testing is seen as more efficient and potentially less costly.

Because multiplex tests involve multiple genes, concerns have been raised that multiplex tests would violate multiple patents on genes and associations.[98] That is, although it is possible that a multiplex test might represent a patentable advance, for the patent holder to practice the

[96] See Recommendation 13 of the report.

[97] The President's Council on Bioethics. (2008). The changing moral focus of newborn screening: an ethical analysis by the President's Council on Bioethics. Chapter Three: The Future of Newborn Screening. For a discussion of the technological development of affordable whole genome sequencing, see Service, R.F. (2006). Gene Sequencing: The Race for the $1000 Genome. *Science* 311:1544-1546.

[98] See, for example, Nicol, D. (2009). Navigating the molecular patent landscape. *Expert Opinion on Therapeutic Patents* 18(5):461-472, p. 468. See also Soini, S., S. Aymé, and G. Matthijs. (2008). Patenting and licensing in genetic testing: ethical, legal and social issues. *European Journal of Human Genetics* 16:S10-S50, p. S12.; Ebersole, T.J., M.C. Guthrie, and J.A. Goldstein. (2005). Patent pools as a solution to the licensing problems of diagnostic genetics. *Intellectual Property & Technology Law Journal* 17:6-13.

invention, rights to all patented genes associated with the test would have to be acquired or licensed. If the relevant patents (or licenses to them) are not all held by the test developer, the development of these tests may not be pursued and their promise could go unrealized. The validity of these concerns is examined in this section.

The first issue to consider in judging whether patents pose a barrier to the development of multiplex tests is whether multiplex methods of testing would likely infringe patent claims to genes and associations. To evaluate that issue, one must understand how multiplex tests are designed. The most common multiplex platform is the gene microarray, which consists of a substrate upon which specific nucleic acid molecules are placed or "spotted." These spotted molecules, which have sequences that correspond to partial gene sequences or sequences of phenotypic relevance outside of genes, will hybridize or combine with complementary patient DNA fragment molecules. This hybridization can be detected by a variety of methods, thus revealing the presence or absence of specific sequences in the patient's genome. A related method of multiplex testing involves microbeads. Like microarrays, microbead systems involve attaching onto beads DNA molecules that correspond to partial gene sequences or sequences of phenotypic relevance outside of genes.

For both microarray and microbead forms of multiplex testing, the probe molecules used to detect gene sequences would infringe corresponding patented genes if the probe molecules are identical or equivalent to the claimed isolated genes. The probe molecules would also infringe any claims to identical or equivalent oligonucleotide molecules useful as probes.[99] Similarly, those spotted molecules whose sequences correspond to DNA sequences of phenotypic relevance outside of genes would infringe patent claims to such molecules. Multiplex testing would also infringe association patent claims. Association patent claims, a phrase used in this report to refer to claims of a simple association between a genotype with a phenotype, may not reference a particular method for detecting the genotype. For example, patent 5,693,470 claims "[a] method of determining a predisposition to cancer comprising: testing a body sample of a human to ascertain the presence of a mutation in a gene identified as hMSH2." Because this patent claims "testing" generally, any testing method, including any multiplex testing that "ascertains the presence" of a mutation in *hMSH2*, probably would infringe this patent claim, so long as the method was used for determining, among other things, a predisposition to cancer. Thus, association patent claims of this nature—which do not specify a particular method for detecting the genotype—likely would be infringed by multiplex testing.

Because multiplex testing methods would infringe typical patent claims on genes and associations, to market a multiplex test without being sued for infringement, a test developer would need to license those patents infringed by the particular molecules used in the multiplex test. The alternative of leaving patented genes out of a multiplex test or not reporting the results pertaining to those genes undermines the very clinical utility of multiplex analysis.[100]

[99] Patent 5,622,829 contains claims to such fragments.

[100] While it may be that not reporting test results prevents the patent holder from becoming aware of the use of patent-protected genes or probe molecules, performance of the test is still infringement so long as the probe molecules used in the test are claimed by the patent or equivalent to what the patent claims.

The number of licenses a microarray developer would need would depend on how many genes the developer intended to include in the test and how many of those genes are protected by patents. But, assuming the developer wanted to test for multiple conditions involving many genes or multiple genes causing one condition, the developer would likely need many licenses given that many human genes are protected by patents. Although studies conducted so far have not been able to determine exactly how many genes in the genome are patented, these studies provide related information that is useful in getting a general sense of just how much of the genome is covered by patents. For example, one study found that 20 percent of the genes identified so far in the human genome are referenced in the claims of patents.[101] This corresponds to 4,382 genes of the 23,688 genes in the National Center for Biotechnology Information's gene database as of 2007.[102] The authors of this study, Kyle Jensen and Fiona E. Murray, determined these numbers by first searching for all patents that include nucleotide sequences in the claims (the claims section of a patent describes what is precisely claimed as the invention) and correlating the sequences with messenger RNAs from the human genome—messenger RNAs are nucleic acid molecules that are made from genes and have a sequence complementary to a gene.[103] The genes referenced in the claims are distributed over 4,270 patents "owned by 1,156 different assignees (with no adjustments for mergers and acquisition activity, subsidiaries, or spelling variations)."[104] Of these patents, 63 percent are assigned to private firms.[105] The limitation of this study is that even when a patent claim contains a nucleotide sequence, it does not necessarily mean that the isolated nucleic acid molecule that corresponds to that sequence is the actual patented invention. In some cases, the patent may be claiming the isolated molecule as the invention, but in other cases, the patent could be claiming something else, such as a process for using the molecule.[106]

Although the Jensen and Murray study cannot be extrapolated to conclude that precisely 20 percent of human genes are either patented as isolated molecules or protected through association patent claims, the study does suggest that a substantial number of genes are protected by patents. Furthermore, ownership of these patents is spread over a large number of assignees. The existence of so many patents protecting genes, spread among various assignees, creates a "patent thicket"—"a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology."[107] To hack through this thicket to develop a multiplex test, a developer would face several challenges. The developer first would have to identify all the patents requiring licenses. This would involve a costly search for relevant patents and an analysis of their claims to determine whether the proposed multiplex test would infringe each particular claim. Once the patents relevant to the test were identified, the developer would have to determine whether licenses were available for each patent. The case

[101] Jensen, K., and F. Murray. (2005). Intellectual property landscape of the human genome. *Science* 310:239-240, p. 239.
[102] Ibid.
[103] Ibid. The researchers specifically conducted a search of the patent database looking for the phrase "SEQ ID NO" in the claims. This phrase stands in for the particular nucleotide sequence that is disclosed later in the patent.
[104] Ibid.
[105] Ibid.
[106] Ibid.
[107] Shapiro, C. (2001). Navigating the patent thicket: cross licenses, patent pools, and standard setting. *Innovation Policy and the Economy* 1:119-150.

studies revealed that such licensing information often is difficult to obtain. Finally, the developer would have to separately negotiate licenses with each individual patent holder.[108]

Assuming the developer could obtain all of the needed licenses, their cumulative cost might make the product unprofitable. As a practical matter, the developer's anticipation of such "royalty stacking" and the transaction costs described above may discourage him or her from pursuing the development of the multiplex test in the first place, with the result that this innovation is not realized for the benefit of patients and that more costly and time-consuming gene-by-gene testing remains the practice.

Instead of trying to obtain multiple licenses, an innovator could ignore the blocking patents, develop the product, and then respond to infringement suits if they ensue. However, this is not an advisable alternative approach. As Ian Ayres and Gideon Parchomovsky have observed, "By sinking money into the commercialization of an infringing product, the cumulative innovator only makes herself an easier prey for patent holders. After an innovation has been commercialized and put to large scale production, patentees can seek far greater royalties by threatening to shut down production."[109]

It can also be difficult for a company to determine whether a product or service will infringe existing patents. This is particularly prevalent in the information technology field.[110] Choosing to proceed with a product involves the risk of being sued, and the expense of defending against suits that arise diverts funds that could otherwise be used for innovation.

When there are many patents that must be licensed for a technology to be commercialized, there is also the risk of a licensing hold-out delaying or blocking commercialization. That is, a patent holder on one small component of the technology may threaten to enjoin the use of his or her patent unless granted a royalty that far exceeds the value of his or her component to the overall product.[111] The developer must either grant the high licensing fee or challenge the motion to enjoin.

The Supreme Court's decision in *eBay v. MercExchange, L.L.C.*, 547 U.S. 388 (2006), may have minimized a hold-out's chances of obtaining such an injunction. Prior to that decision, the Court of Appeals for the Federal Circuit had been applying a rule "that courts will issue permanent

[108] Ayres, I. and G. Parchomovsky. (2007). Tradable patent rights: a new approach to innovation. *Scholarship at Penn Law.* Paper 183. available at http://lsr.nellco.org/upenn_wps/183
[109] Ayres, I. and G. Parchomovsky, op. cit., p. 17.
[110] Testifying before the Federal Trade Commission, a representative of Cisco systems stated that "the large number of issued patents in our field [information technology] makes it virtually impossible to search all potentially relevant patents, review the claims, and evaluate the possibility of an infringement claim or the need for a license." *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy: A Report by the Federal Trade Commission*. October 2003, http://www.ftc.gov/os/2003/10/innovationrpt.pdf.
[111] Lemley, M.A. and C. Shapiro. (2007). Patent Holdup and Royalty Stacking. Texas Law Review 85:1991-2049. A threat to enjoin involves a threat to petition the court for an injunction, an injunction being a declaration by the court requiring a party to do or not do some particular act. In this case, the patent holder would threaten to seek an injunction declaring that the developer could not use the patented component.

injunctions against patent infringement absent exceptional circumstances."[112] The Supreme Court rejected this rule, holding that a four-part test applies to decisions whether to grant permanent injunctions.[113] Under that test,

> A plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction.[114]

In a concurring opinion in *eBay*, Justice Kennedy recognized the phenomenon of holdouts seeking to extract exorbitant licensing fees and suggested that injunctive relief may not be appropriate in such cases: "When the patented invention is but a small component of the product the companies seek to produce and the threat of an injunction is employed simply for undue leverage in negotiations, legal damages may well be sufficient to compensate for the infringement and an injunction may not serve the public interest."[115]

Despite this encouraging language, how the *eBay* four-factor test would be applied to a patent holder who sought to enjoin commercialization of a multiplex test is unclear. This uncertainty has a chilling effect; that is, under *eBay* a multiplex developer does not learn until after lengthy and expensive litigation is concluded whether the test will be enjoined. The risk that it will be is likely to discourage investment in such tests.

Holdouts create problems not only when they threaten an injunction for the purpose of negotiating a higher licensing fee, but also when they refuse to license at all. Faced with such a situation, a multiplex test developer likely would have little legal recourse. Such a developer might be inclined to sue the holdout on the theory that his refusal to license was an antitrust violation. However, based on the U.S. Supreme Court's ruling in *Verizon Communications Inc. v. Law Offices of Curtis V. Trinko, L.L.P.*, 540 U.S. 398 (2004), trial courts likely would not find such a refusal to license to be anticompetitive under § 2 of the Sherman Act.[116] For that reason as well, the Government is unlikely to prevail in court if it seeks criminal or civil sanctions for anticompetitive behavior against a holdout that refuses to license. Therefore, any threat by the Government to bring criminal or civil sanctions against a holdout that refused to license would probably not be credible or effective in motivating the holdout to license.

Thus, the thicket of patents on genes and associations presents multiple challenges that may prevent the development of multiplex tests. Several scholars and companies have echoed these concerns. For example, Dianne Nicol has highlighted several of the challenges discussed here:

[112] MercExchange, L.L.C. v. eBay, Inc., 401 F.3d 1323, 1339 (Fed Cir. 2005).
[113] *eBay v. MercExchange, L.L.C.*, 547 U.S. 388 (2006)
[114] Ibid.
[115] Ibid.
[116] Carrier, M.A. (2006). Refusals to license intellectual property after *Trinko*. *DePaul Law Review* 55:1191-1210.

> Companies involved in the development of microarray technology, which allows for multiple tests to be undertaken, are likely to face the greatest level of complexity. If such companies wish to ensure freedom to operate, they have to undertake onerous search obligations to ascertain which patents contain relevant claims and then enter into multiple licensing negotiations. The risks of royalty stacking . . . in such an environment are particularly high. It is not surprising that leaders in the field such as Affymetrix rail against gene and related patents.[117]

Affymetrix is a company that has developed a platform microarray for multiplex tests.[118] Another company involved in developing platforms for multiplex testing, Illumina, also raised concerns in a public comment about patents affecting the development of multiplex tests. In its public comment on the draft form of this report, the company expressed support for gene patenting, but pointed out that "[d]ealing with such vast amounts of genetic information has the potential to raise a whole host of unique intellectual property challenges . . . ."

Gert Matthijs, Ségolčne Ayme, and Sirpa Soini, writing on behalf of the European Society of Human Genetics, have also expressed concerns: "Biochip development will enable rapid detection of hundreds of genetic mutations, but practicing this might also violate hundreds of patents."[119]

What some scholars call a patent thicket is described by others as an "anticommons problem." The term "anticommons" is a shorthand reference to the phrase "the tragedy of the anticommons," which itself is a play on the older expression "the tragedy of the commons." The scholar who coined the phrase, Michael Heller, explained the derivation this way:

> In a commons, by definition, multiple owners are each endowed with the privilege to use a given resource, and no one has the right to exclude another. When too many owners have such a privilege of use, the resource is prone to overuse—*a tragedy of the commons*. Canonical examples include depleted fisheries, overgrazed fields, and polluted air.
>
> In an anticommons, by my definition, multiple owners are each endowed with the right to exclude others from a scarce resource, and no one has an effective privilege of use. When there are too many owners holding rights of exclusion, the resource is prone to underuse—*a tragedy of the anticommons*.[120]

Rebecca Eisenberg recently wrote about the possibility of an anticommons problem in multiplex testing: "some DNA diagnostic products, such as microarrays that include many different genes and mutations, could face an anticommons problem if the burden of negotiating many necessary

[117] Nicol, D. (2009). Navigating the molecular patent landscape. *Expert Opinion on Therapeutic Patents* 18(5):461-472, p. 468.
[118] Add citation.
[119] Soini, S., S. Aymé, and G. Matthijs. op. cit.
[120] Heller, M.A. (1998). The tragedy of the anticommons: property in the transition from Marx to markets. *Harvard Law Review* 111:621-688.

licenses [from each patent owner] consumes too much of the expected value of the product. This may be why microarray developer Affymetrix has been an outspoken opponent of patents on DNA sequences."[121]

Indeed, as articulated earlier in this report, the numerous existing patent claims on genes are already affecting the use, if not the development, of multiplex tests in that clinicians are not reporting the results for patent-protected genes in multiplex tests for fear of inviting a lawsuit.

Earlier Patent Thickets and Approaches to Addressing Them

The thicket of patents on genes and associations is not the first thicket to arise during the history of the U.S. patent system. One of the earliest documented patent thickets arose in the 1850s when various patents on components of the sewing machine temporarily prevented its development.[122] Eventually, the various patent holders formed a patent pool to consolidate their rights so that they could proceed with development of the sewing machine.[123]

Cumulative technologies such as the sewing machine—that is, inventions made up of several components or elements—often result in patent thickets because different parties may have patented the various components. Other examples of cumulative technologies where patent thickets developed include radio and airplanes in the early 20th century.[124] In the case of radio, Robert Merges and Richard R. Nelson explain that "the presence of a number of broad patents, which were held by different parties and were difficult to invent around, interfered with the development of the technology."[125] In the end, the various patent holders formed Radio Corporation of America (RCA) to break the deadlock.[126] In the case of the airplane patent thicket, the Secretary of the Navy had to intervene, working out a deal to allow automatic cross-licensing.[127] This solution, according to a group of officials with the United States Patent and Trademark Office, "was crucial to the U.S. Government because the two major patent holders, the Wright company and the Curtiss Company, had effectively blocked the building of any new airplanes, which were desperately needed as the United States was entering World War I."[128]

Patent pools are thus one possible solution to patent thickets. Birgit Verbeure and her coauthors have defined a patent pool as an agreement "between two or more patent owners to license one or more of their patents as a package to one another, and to third parties willing to pay the

[121] Eisenberg, R. (2008). Noncompliance, nonenforcement, nonproblem? Rethinking the anticommons in biomedical research. Houston Law Review 45:1059-1099, p. 1072.
[122] Mossoff, A. (2009). A stitch in time: the rise and fall of the sewing machine patent thicket. *George Mason University Law and Economics Research Paper Series*, 09-19. p. 4.
[123] Add Mossoff page cite.
[124] Merges, R.P., and R.R. Nelson. (1990). On the complex economics of patent scope. *Columbia Law Review* 90:839-916
[125] Ibid. p. 892-93
[126] Ibid. p. 893
[127] Ibid. p. 891
[128] Clark, J., J. Piccolo, B. Stanton, and K. Tyson. (2000). Patent pools: a solution to the problem of access in biotechnology patents? Report from the United States Patent and Trademark Office.

associated royalties."[129] Because members of the pool or outsiders can obtain all needed patents with one license, the problem of royalty stacking is solved.[130] The ability to obtain all patents with one license also reduces the transaction costs that would result if a developer had to separately negotiate multiple licenses. The members of the pool agree to a formula for distributing royalties among themselves from licenses.[131] Other benefits of patent pools include the avoidance of costly litigation over patent rights and the sharing of technical information among the members of the pool.[132]

Patent pools have proven successful in solving patent thickets in the field of electronic technologies, a field in which the need to standardize technologies for interoperability creates an incentive to pool that does not exist in biotechnology.[133] Nonetheless, a few patent pools have formed in biotechnology, particularly in the agricultural arena, including one pool involving crucial patents for Golden Rice.[134] But even in agriculture, pools have yet to provide a full solution to the patent thicket problem.[135]

Patent pools have also formed when no single patent holder could bring a product to market without licenses from all of the other patent holders; this was why a patent pool formed for radio, as described earlier. However, the holder of an important patent claim on a gene or association can often exploit the patent on its own, making and offering a genetic test protected by the patent. Such a patent holder's refusal to participate in a pool could prevent its formation or limit its usefulness.[136] And, as noted earlier, because of *Verizon Communications Inc. v. Law Offices of Curtis V. Trinko, L.L.P.,* threats to sue a hold-out for anti-competitive activity in such a situation likely would not be effective.

Although the holder of a patent on an important gene can exclusively market a genetic test for the condition or conditions that gene is associated with, such a patent holder, according to Ted Ebersole, Marvin Guthrie, and Jorge Goldstein, would have an incentive to join a patent pool if patents on other mutations involved in the particular condition were held by others.[137] Goldstein and his coauthors elaborate that if, under these circumstances, an organization such as the American College of Medical Genetics (ACMG) defined the particular genes needed to be tested for the specific condition, the holders of patents on important mutations would "recognize how crucial it is that all of these mutations be tested simultaneously and offer assistance [to one another] by agreeing to participate in a patent pool."[138]

[129] Verbeure, B., E. van Zimmeren, G. Matthijs, and G. Van Overwalle. (2006). Patent pools and diagnostic testing. *Trends in Biotechnology* 24(3):115-20, p. 117.
[130] Clark, J., J. Piccolo, B. Stanton, and K. Tyson. op. cit.
[131] Verbeure, B., E. van Zimmeren, G. Matthijs, and G. Van Overwalle. op. cit.
[132] Ibid.
[133] Ibid.
[134] Ibid.
[135] Wright, B.D. and P.G. Pardey. (2006). Changing Intellectual Property Regimes: Implications for Developing Country Agriculture. 2. *International Journal of Technology and Globalisation* 2:93-114.
[136] Ibid.
[137] Ebersole, T.J., M.C. Guthrie, and J.A. Goldstein. Op. cit.
[138] Ibid. P. 11.

Although the existence of these circumstances would seem to create an incentive to join a patent pool, these circumstances were generally not found in the case studies. For example, Myriad Genetics has patent rights to all those breast cancer mutations that, for the moment, appear relevant for testing. Similarly, one party, Athena Diagnostics, holds patents rights on two important mutations associated with hearing loss, while other common mutations that have been discovered are not patented. As such, Athena is in a position to test for all common mutations, but prevent anyone else from doing so. Unlike the patents on mutations associated with breast cancer and hearing loss, patents on mutations associated with LQTS are now held by two different parties. Cross-licenses, rather than a patent pool, would seem to be a straightforward solution to permit each rights holder to offer complete testing, but it is not clear yet if this will happen.

Another challenge to setting up a patent pool is that it must not be anticompetitive in operation. The Department of Justice and the Federal Trade Commission have issued guidelines on what kinds of pooling practices qualify as competitive and anti-competitive.[139]

In sum, patent pooling shows some promise as a solution to the patent thicket that threatens the development of multiplex testing. However, there has been little progress to date in demonstrating the utility of the approach and thus doubts remain about the viability of patent pooling as a solution in the area of genetic testing.

A royalty-collection clearinghouse has also been proposed by Birgit Verbeure and her coauthors as a potential solution to patent thickets in genetics.[140] A patent clearinghouse would involve patent owners granting the clearinghouse the right to set license terms; the clearinghouse would then set a standard patent licensing fee, which would eliminate transaction costs because there would be no negotiation..[141] The clearinghouse would collect royalties from the licensees, paying patent holders according to an agreed-upon formula after deducting administrative costs.[142] To solve the royalty stacking problem, a clearinghouse could use "royalty stacking clauses" in their licensing agreements that would reduce or cap royalties for those who took many licenses.[143]

To be effective, clearinghouses must involve an entire branch of industry or many patent holders.[144] This challenge as well as others led Verbeure to conclude that it "remains to be seen whether patent proprietors with a strong portfolio would be willing to voluntarily participate in such a far reaching model, where patent holders no longer have ultimate

[139] Clark, J., J. Piccolo, B. Stanton, and K. Tyson. op. cit.
[140] Van Overwalle, G., E. van Zimmeren, B. Verbeure, and G. Matthijs. (2007). Dealing with patent fragmentation in ICT and genetics: patent pools and clearinghouses. *First Monday* 12(6). Available at http://firstmonday.org/htbin/cgiwrap/bin/ojs/index.php/fm/article/view/1912/1794
[141] Nielsen, C.M. and M.R. Samardzija. (2007). Compulsory patent licensing: is it a viable solution in the United States? *Michigan Telecommunications Technology Law Review* 13:509-539, p. 532.
[142] van Zimmerman, E., B. Verbeure, G. Matthijs, G. Van Overwalle. (2006). A clearing house for diagnostic testing: the solution to ensure access to and use of patented genetic inventions? *Bulletin of the World Health Organization* 84(5). Available at http://www.scielosp.org/scielo.php?pid=S0042-96862006000500013&script=sci_arttext
[143] Ibid.
[144] Ibid.

control over all transactions with regard to their patented technologies managed by the clearing house."[145] Thus, as with patent pools, questions remain concerning the viability of this approach to addressing patent thickets.

The Potential Effect of Patents and Licensing Practices on Clinical Whole Genome Sequencing

As noted in the introduction to this section, affordable clinical whole genome sequencing is on the horizon. Once it is developed, clinicians hope to use a patient's genomic information to guide near-term preventive strategies and treatment decisions. Given the promise of affordable whole genome sequencing, the Committee explored whether a patent thicket could delay or prevent the development of this technology. In other words, would whole genome sequencing infringe the majority of existing patents on isolated genes and association patent claims?

To answer that question, one must consider how whole genome sequencing is accomplished. A variety of methods exist, but most rely on the massively parallel amplification and analysis of small sections of the genome and then assembly of the resulting sequences by sophisticated IT algorithms.[146]

The question then becomes whether such a process would infringe typical claims to isolated genes and association patent claims. Although it is difficult to generalize, claims to isolated genes typically claim the isolated gene and various complementary probes; the gene might be claimed either in its cDNA form or as a whole gene sequence, including non-coding sequences, or both.

At this time, there is uncertainty in the legal community concerning whether whole-genome sequencing would infringe patent claims on genes. Furthermore, differences in claim language among patent claims on genes may lead to differing infringement determinations. However, because of the distinct possibility that some patent claims on genes will be infringed by whole-genome sequencing, these patents remain a concern as a potential barrier to the development of whole-genome sequencing.

While uncertainly exists as to whether patent claims on specific isolated genes would be infringed by whole-genome sequencing, one can be more confident that association patent claims would be infringed by whole-genome sequencing. Association patent claims can be quite broad. Consider the first two claims in U.S. patent 5,508,167, relating to a protein associated with the development of Alzheimer disease:

> 1. A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease (AD) comprising directly or indirectly: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE2) in the subject; and observing whether or not the subject is at increased risk of developing late

[145] Van Overwalle, G., E. van Zimmeren, B. Verbeure, and G. Matthijs. op. cit.
[146] Mardis, E. (2008). The impact of next-generation sequencing technology on genetics. *Trends in Genetics* 24(3):133-141.

> onset AD by observing if the presence of ApoE4 is or is not detected, wherein the presence of ApoE4 indicates said subject is at increased risk of developing late onset AD.
>
> 2. A method according to claim 1, wherein said detecting step is carried out by collecting a biological sample containing DNA from said subject, and then determining the presence or absence of DNA encoding ApoE4 in said biological sample.

These claims do not refer to particular molecular methods of detecting a gene or protein's presence. Thus, the claims could be interpreted as protecting multiple, unspecified methods, which would include whole genome sequencing (as well as multiplex testing). Whole genome sequencing and multiplex testing would appear to infringe these claims because, consistent with dependent claim 2, both methods would involve collecting a biological sample and determining the presence of DNA encoding ApoE4. The infringement of this claim, however, would further depend on using the presence of the gene to infer that the patient was at increased risk for late-onset Alzheimer disease. If other association patent claims have a breadth similar to the above claims, association patent claims may create a patent thicket that challenges the development of whole-genome sequencing.[147]

Finally, before whole genome sequencing is performed routinely in the clinical diagnostic laboratory, it is likely that parallel sequencing of multiple genes will be routinely performed. This process relies on oligonucleotides—small nucleic acid molecules—that include partial or complete gene sequences that are typically protected by patent. Therefore, the use of these oligonucleotides may well infringe patent claims on probe molecules or genes, and these patents may create a thicket that prevents or delays the development of parallel sequencing of multiple genes.

As in the case of multiplex tests, patent pools and clearinghouses are potential solutions to any thickets that arise in the area of whole genome sequencing or parallel sequencing of multiple genes, but questions remain as to the viability of these potential solutions.

Test Developers Have Limited Protection from Infringement Liability

The challenges patents pose to innovations in testing are not limited to patent thickets and their associated problems. Patents can also constrain developers' ability to conduct research needed to create new innovations.

Existing exemptions from liability for patent infringement provide only limited protection to those who wish to use patent-protected isolated gene molecules or associations during research

[147] Unlike patents on associations, patents on platform technologies for sequencing and algorithms used to correctly order the sequence data can be invented around. So, these patents do not appear to pose as substantial a barrier to clinical access to whole genome sequencing. That is, a laboratory that was not licensed rights to a particular patented platform could rely on another platform or develop its own platform for whole genome sequencing. Indeed, several competing proprietary whole genome sequencing platforms already exist.

and experimentation to develop improved genetic tests. First, the common law experimental use exemption most likely would not protect test developers from liability for using patent-protected isolated gene molecules or associations in the course of developing a new test. The narrow exemption is limited to "actions performed 'for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.'"[148] The exemption does not extend to research and experiments that have "definite, cognizable, and not insubstantial commercial purposes."[149] Furthermore, the Federal Circuit has held that, regardless of whether the use is ultimately for commercial gain, any experimental use "in keeping with the legitimate business of the alleged infringer does not qualify for the experimental use defense."[150] In *Madey v. Duke University*, the Federal Circuit described Duke University's legitimate business as "educating and enlightening students and faculty participating in . . . [research] projects."[151]

Given these limitations on the experimental use exception, neither academic medical centers nor companies are likely to be able to invoke it to protect any infringing acts they committed in the course of experiments to develop a new genetic test. An example is provided by a developer creating a multiplex test that includes a patented gene fragment. Experiments to develop and validate this test might involve testing patients or known samples to verify the test's performance. Such experiments would necessarily involve the use of the patent-protected gene fragment. Validation of the test by testing patients would also likely infringe any patent claims to testing patients and associating the designated gene with a phenotype. In the case of an academic medical center, such uses of the patented gene fragments and associations would be arguably commercial in nature because any test that was ultimately developed from these experiments would be offered as a testing service. And even if this use somehow was not commercial, one could argue that the use of the gene fragment or association to develop a genetic test would not be eligible for the exemption because it would relate to the legitimate business of an academic medical center in developing clinically useful diagnostics that improve patient care. In the case of companies using a patented gene fragment in the course of experiments to develop tests that involve those fragments, such experimental use would almost certainly be commercial in purpose and related to the company's business of developing biotechnology products or services; in that case, the company would not be entitled to the exemption.

One jurist has observed that such limitations on research are at odds with the role of patents in disclosing knowledge:

> The purpose of a patent system is not only to provide a financial incentive to create new knowledge and bring it to public benefit through new products; it also serves to add to the body of published scientific/technologic knowledge. The requirement of disclosure of the details of patented inventions facilitates further

[148] *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2003) (quoting *Embrex, Inc. v. Service Engineering Corp.*, 216 F.3d 1343 (Fed. Cir. 2000).
[149] *Embrex, Inc. v. Service Engineering Corp.*, 216 F.3d 1343 (Fed. Cir. 2000)
[150] *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2003). Even if one were to argue that *Madey's* interpretation of experimental use was confined to research tools such as the invention used in *Madey*, genes claimed in some patent claims can serve as research tools in some contexts.
[151] Ibid.

> knowledge and understanding of what was done by the patentee, and may lead to further technologic advance. The right to conduct research to achieve such knowledge need not, and should not, await expiration of the patent. That is not the law, and it would be a practice impossible to administer. Yet today the court disapproves and essentially eliminates the common law research exemption. This change of law is ill-suited to today's research-founded, technology-based economy.[152]

While the common law experimental use exemption likely would not provide any protection to genetic test developers, a statutory experimental use exemption likely provides only limited protection. This statutory exemption is found in the Hatch-Waxman Act and provides an exemption from patent infringement liability for using a patented invention for the purpose of developing and submitting information under a Federal law regulating drugs.[153] Given the conditions needed to invoke this exemption, it appears that only test kit developers, and not creators of laboratory-developed tests, may be able to invoke it because test kits, unlike laboratory-developed tests, are subject to approval by the FDA as medical devices under the Food, Drug, and Cosmetic Act.[154] To gain approval for a genetic test kit, the test developer would have to demonstrate the test's analytical validity, which would require performing the kit's genetic test on patients.[155] Because in this case the performance of the genetic test would be related to submitting information under the FDCA for approval of the test kit, the use of the patented isolated gene molecules and patented associations would likely be exempt from infringement liability.[156] However, once the genetic test kit was approved and then marketed, the use of the patented isolated gene molecules and patented associations without a license would no longer be exempt from infringement.

Unlike test kits, laboratory-developed tests are presently regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a. Because CLIA is not a Federal law that regulates drugs, any clinical testing done as research to develop a CLIA-approved testing service would not fit within the Hatch-Waxman exemption.[157]

The majority of genetic tests are offered as laboratory-developed tests, rather than as testing kits.[158] Unless this trend changes, very few genetic test developers (i.e., only those creating kits) will able to conduct developmental research on patents without being liable for infringement.

In sum, the public comments and the experience of experts among the Committee suggest that test manufacturers are eager to develop—and clinicians are eager to use—multiplex tests, rather

[152] *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 873 (Fed. Cir. 2003) (Newman, J., dissenting). The case did not involve the common law research exemption—instead, it was about the statutory research exemption, which is discussed in subsequent paragraphs of this report.
[153] 35 U.S.C. § 271(e)(1)
[154] 21 U.S.C. § 321(h); 21 C.F.R. Part 809
[155] See FDA Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm#8
[156] See Kane, E.M., op.cit. p. 843.
[157] Kane, E.M., op.cit. p. 844.
[158] Ibid. p. 839.

than single-gene tests, to carry out genetic testing. These tests would be more efficient than conducting a series of individual tests. Patent claims on isolated genes and association patent claims, however, appear to have already created a thicket of intellectual property rights that may prevent innovators from creating these multiplex tests. Similar concerns arise when envisioning the clinical application of whole genome sequencing. Such scenarios threaten to diminish the usefulness of these promising technologies and their application to patient care. The creation of a patent pool or clearinghouse is a possible, but uncertain, solution to the patent thicket facing multiplex tests and whole genome sequencing.

More information is needed on patent holders' licenses: particularly the types of licenses that have been issued and whether they are restricted to a particular field of use. Such information would enable technology developers to more easily determine the necessary licenses for planned innovations. As multiplex testing and whole genome sequencing become commonplace in medicine, challenges to innovators obtaining access to information may discourage the development of advanced tests and their application to medicine.

VI. RELEVANT LEGAL DEVELOPMENTS

The Committee also considered legal developments in the patent arena and how they might affect the identified issues. Several public commenters were of the view that recent legal decisions have obviated any need for change; others suggested that the decisions did not alter what were viewed as existing threats to patient access.

ACLU Challenges the Patentability of Nucleic Acid Molecules

The Association for Molecular Pathology and other plaintiffs, represented by the American Civil Liberties Union and the Public Patent Foundation, recently filed a lawsuit that challenges the idea that isolated nucleic acid molecules are patentable subject matter. This will be the first case to squarely consider whether such molecules are patentable subject matter.

Congressional committee reports accompanying the Patent Act of 1952 indicate that Congress intended patentable statutory subject matter under § 101 to "include anything under the sun that is made by man."[159] On the other hand, things that are not made by humans—such as laws of nature (for example, the law of gravity), natural phenomena, and abstract ideas—are not patentable subject matter under § 101.[160] This exclusion extends to products of nature, such as minerals.[161] Based on this legal principle, the genes found in nature—the genes within a human's cells, for example—cannot be patented. However, the USPTO begin issuing patents on isolated nucleic acid molecules whose sequences correspond to genes in 1992 and, in response to public

[159] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[160] Ibid. No major opinion apparently has addressed whether the exclusion of laws of nature from patent-eligibility is constitutionally mandated, although this may be the case, because patents on laws of nature would not serve to promote the progress of useful arts. For a fuller discussion of this issue, see Gipstein, R.S. (2003). The isolation and purification exception to the general unpatentability of products of nature. *Columbia Science and Technology Law Review* 4:242. Justice Breyer, in his dissent from the denial of certiorari in *Lab. Corp. v. Metabolite*, 548 U.S. 124 (2006), implies that the exclusion of laws of nature from patentability is constitutionally mandated.
[161] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

comments, has expressed its belief that these isolated molecules are patentable as compositions of matter or as manufactures because they do not exist in a purified, isolated form in nature.[162]

Among the cases the USPTO cites in support of its conclusion is the 1911 case *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911). In that case, Judge Learned Hand held that adrenaline purified from a gland was patentable. In finding the invention patentable, Judge Hand reasoned that purified adrenaline differed "not in degree, but in kind" from the adrenaline found in glands and was "for every practical purpose a new thing commercially and therapeutically."[163]

Since *Parke-Davis*, other courts have found inventions derived from nature to be patentable.[164] In *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)—another case cited by the USPTO in support of its conclusion—the U.S. Supreme Court considered a different inquiry: whether a living thing that did not occur naturally was patentable. A case that was closely watched by the biotechnology community, *Charkrabarty* concerned the patentability of a bacterium that had been genetically altered by introducing plasmids that enabled it to degrade oil.[165] The Supreme Court held that the bacterium qualified as a patentable manufacture or composition of matter because it was "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility."[166] The Court continued, "[The inventor's] discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101."[167]

[162] "The first patented gene was the retinoblastoma tumor suppressor gene . . . ." Koss, C. (2007). Oysters and oligonucelotides: Concerns and proposals for patenting research tools. *Cardozo Arts & Entertainment Law Journal* 25:747-773, p. 753, note 40. The U.S. Patent and Trademark Office's (USPTO's) utility guidelines reveal the basis for the USPTO's belief that isolated, purified DNA molecules are patentable. The guidelines are available at http://www.uspto.gov/web/offices/com/sol/og/2001/week05/patutil.htm. Purification and isolation here refer not to absolute purity, but to the general absence of other large molecules and biological substances. See Chin, A. (2006). Artful prior art and the quality of DNA patents. *Alabama Law Review* 57:975.

[163] *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911).

[164] For example, in *Merck & Co., Inc. v Olin Mathieson Chemical Corporation*, 253 F.2d. 156 (4th Cir. 1958), vitamin B12, extracted from the liver of cattle, was found to be patentable. At least some cases before *Parke-Davis* that considered whether claimed inventions derived from nature were patentable found that they were not patentable—see, for example, *American Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874) (holding that pulp purified from wood and other sources was not a new manufacture). Even some cases after *Parke-Davis* found such inventions not to be patentable—see, for example, *General Electric Co. v. DeForest Radio Co.*, 28 F.2d 641 (3d. Cir. 1928) (holding that purified tungsten was not patentable, even though it has ductility and strength that natural tungsten oxide lacks). Different perspectives on the evolution of "products of nature" jurisprudence can be found in Gipstein, Conley (Parts I and II), and in Andrews, L. J. Paradise. (2008). Genetic Sequence Patents: Historical Justification and Current Impacts. Paper presented at the Conference on Living Properties: Making Knowledge and Controlling Ownership in the History of Biology. Berlin, Germany, available at http://www.kentlaw.edu/islat/pdf/GeneticSequencePatents.pdf. A complete review of these cases is beyond the scope of this report.

[165] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[166] Ibid.

[167] Ibid.

The *Chakrabarty* decision signaled to the biotechnology community that genetically altered organisms could be patented. No case, however, has squarely considered the question of whether isolated, purified nucleic acid molecules are patentable subject matter.[168]

John Conley and Roberte Makowski have critiqued USPTO's conclusion for suggesting that the purification of naturally occurring substances automatically confers patentability.[169] Conley and Makowski argue that the focus of the patentability inquiry, as established in *Parke-Davis* and *Charkrabarty*, is not on purification *per se*, but on whether an invention derived from nature differs "in some substantial and material way from the natural version."[170] In other words—using the language from *Parke-Davis*—the invention must be different "in kind." Therefore, according to Conley and Makowski, purification "is a basis for patentability only if it creates a material difference between the claimed product and its natural precursor."[171] Conley and Makowski point to arguments that could be made both for and against the patentability of isolated nucleic acid molecules and have called for the courts to conduct a "fact-specific inquiry into the materiality of the differences that are created by the processes such as isolation, purification, and synthesis."[172]

The Association for Molecular Pathology's recently filed lawsuit presents an opportunity for the Federal courts to undertake this inquiry, as well as to consider whether association patent claims are patentable.[173] The plaintiffs are challenging the validity of patents associated with two genes used in breast cancer genetic testing, specifically *BRCA1* and *BRCA2*.[174] In the complaint filed with the United States District Court, Southern District of New York, the plaintiffs argue that patents on isolated nucleic acid molecules and association patent claims violate "long established principles that prohibit the patenting of laws of nature, products of nature, and abstract ideas."[175]

---

[168] Conley, J.M., and R. Makowski (Part II), op. cit.; Berman, H., and R. Dreyfuss, op. cit. In a case that came close to this question but that did not address it, the Federal Circuit considered various other challenges to a patent claiming a purified and isolated DNA molecule. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991).

[169] For such a critique, see Conley and Makowski (Part II), op. cit.

[170] Ibid. p. 379. See also Chisum, D.S., *Chisum on Patents* (2001 & Supps.) (recognizing that in *Parke-Davis*, the focus of the patentability inquiry is on whether the pure compound differs in kind). See also Berman and Dreyfuss, op. cit. (recognizing that, to be patentable, an invention derived from nature must be different in kind from the product of nature). Conley and Makowski's statement that the invention must have material differences over the product of nature is simply a way of rephrasing the *Parke-Davis* requirement that the invention differ in kind from the product of nature.

[171] Conley, J.M., and R. Makowski (Part II), op. cit.

[172] Ibid. p. 393-394.

[173] The case is not limited to those Myriad patents claiming isolated DNA molecules. It also challenges patents that claim methods of associating a genotype with a phenotype. For example, claim 2 of patent 6,033,857 claims "[a] method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer."

[174] Gene Patents Stifle Patient Access To Medical Care And Critical Research. ACLU Press Release, May 12, 2009, available at http://www.aclu.org/freespeech/gen/39572prs20090512.html

[175] ACLU Compl. ¶ 4, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf

Defendants in the lawsuit include Myriad Genetics, the exclusive licensee of patents associated with breast cancer genetic testing, and the USPTO.

At this writing, this case, *Association for Molecular Pathology, et al. v. United States Patent and Trademark,* has not been decided. If the defendants prevail, the Committee's recommendation will still be relevant because gene patents and associations will remain enforceable. But even if the plaintiffs prevail, the decision would not necessarily lead to the automatic invalidation of all existing patents on genes and associations.[176] Depending on how the decision is framed, there may be a continuing need to challenge patenting strategies.

Recent Case Law Relevant to Association Patent Claims

While the *Association for Molecular Pathology* case goes forward, the U.S. Supreme Court has agreed to review a case that may bear on the patentability of association patent claims. Before reviewing this case, this section provides some background on these patents and the controversy they have provoked.

As noted in the Introduction, novel, useful, and nonobvious processes are eligible for patents. Relying on this, researchers who have discovered associations between particular gene variants and disease have obtained patent claims upon processes involving simply associating a genotype with a phenotype.

Critics of the patenting of such associations argue that process claims of this nature should not be patent-eligible because they involve unpatentable fundamental laws of nature—namely, the relationship or association between a particular genetic sequence and a disease. Furthermore, it can be argued that such processes involve mental steps that are not subject to protection.[177] Whether the courts will agree with these arguments is unclear at the moment. In a recent case, *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), the Federal Circuit Court of Appeals defined the test that governs whether a process qualifies as patent-eligible subject matter under 35 U.S.C. § 101 or is unpatentable as a law of nature. Citing U.S. Supreme Court precedent, the court first recognized that processes that involve a specific application of an abstract idea or natural law are patent-eligible, even though abstract ideas and natural laws themselves are not patentable.[178] The court then elaborated that a process is limited to a specific application of an abstract idea or natural law (and thus patentable) if (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing.[179]

[176] As the attorney for the plaintiffs explained in a recent interview, "Success in this case will encourage new lawsuits regarding any or all of those [existing] patents [on genes]. Theoretically, the facts in each instance are sufficiently different so that there would be no across-the-board invalidation of the patents. Each case would be separate." Albainy-Jenei, S. (2009). Bulletproof: Interview with ACLU attorney Chris Hansen over gene patents. Patent Baristas web site, November 12, 2009. http://www.patentbaristas.com/archives/2009/11/12/bulletproof-interview-with-aclu-attorney-chris-hansen-over-gene-patents/

[177] "Mental processes" is a phrase that has been used by the Federal Circuit in referring to unpatentable processes based solely on mental operations. *In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007).

[178] *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008).

[179] Ibid.

The patented process in question in *Bilski* was not a process for simply associating a genotype with a phenotype, but "a method of hedging risk in the field of commodities trading."[180] Whether a typical claim to a method of diagnosis based on associating a genotype with a phenotype would pass the "machine-or-transformation" test is an open question. The answer will depend on how patent examiners and courts interpret the precise meaning of "machine" and "transformation." The *Bilski* court indicated that future decisions will refine "the precise contours" of what qualifies as a machine or apparatus.[181] Guidance from the court is needed as well on what qualifies as a transformation.[182]

Although the majority opinion in *Bilski* did not reference diagnostic tests, Judge Rader filed a separate opinion in which he commented on the patentability of association patent claims.[183] First, however, Judge Rader rejected the court's "machine-or-transformation" test.[184] He argued that the court's test imposes conditions on the patentability of processes that have no basis in the Patent Act.[185] He elaborated, "[T]he only limits on eligibility [for patents] are inventions that embrace natural laws, natural phenomena, and abstract ideas."[186] Rader then went on to explain that although biological relationships cannot be patented because they are natural laws, processes that employ these relationships for a specific useful end can be.[187]

Therefore, under Judge Rader's analysis, a process for diagnosing a disease based on the biological relationship between a gene and a disease would be patentable. Since his views were in a separate opinion, they do not establish legal precedent. As such, for the moment, no court decision has directly answered whether association patent claims qualify as patentable subject matter or are unpatentable laws of nature.

Following the Federal Circuit's decision, the patent applicants in *Bilski* petitioned the U.S. Supreme Court for a writ of certiorari—that is, they petitioned the Court to review the appellate court's decision.[188] The petitioners asked the Court to decide whether the Federal Circuit's "machine-or-transformation" test for patentable processes was in error.[189] On June 1, 2009, the Court granted the petition, and on November 9, 2009, the Court heard oral argument; the Court is expected to issue a decision by June 2010.[190]

[180] Ibid.
[181] Ibid.
[182] *Patentable Subject Matter: In re Bilski*, Edwards Angell Palmer & Dodge Client Advisory, December 2008, http://www.eapdlaw.com/newsstand/detail.aspx?news=1435
[183] *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008).
[184] Ibid.
[185] Ibid.
[186] Ibid.
[187] Ibid.
[188] *Bilski v. Kappos*, Petition for a Writ of Certiorari, available at http://www.patentlyo.com/bilskipetition.pdf
[189] Ibid.
[190] *In re Bilski,* 545 F.3d 943 (Fed. Cir. 2008), cert. granted sub nom., *Bilski v. Kappos*, 129 S.Ct. 2735 (U.S. June 1, 2009) (No. 08-964). IP Update – Bilski v. Kappos, http://www.finnegan.com/IPUpdateBilskivKappos/

The principles of the Court's decision may be applicable to association patents, and, even if they are not, the Court's decision may offer *dicta*—non-binding statements not needed for the decision—on whether association patent claims are patentable.

To date, the only Supreme Court opinion to comment on the patentability of association patent claims was a 2006 dissent by Justice Stephen Breyer. Breyer filed his dissent to the Court's decision to pass on deciding a case, *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 370 F.3d 1354 (2004), that concerned the validity of an association patent claim.[191] The association patent claim in question in *Lab. Corp.* consisted of assaying a body fluid for homocysteine and then correlating an elevated level of homocysteine with a vitamin B deficiency.[192] The university doctors who patented this process had discovered the biological relationship between these two substances.[193] When the case was before the Federal Circuit Court of Appeals, the Federal Circuit did not reach the issue of the patentability of the process, deciding the case on other grounds.[194] LabCorp sought review of the case by the U.S. Supreme Court, but the Court dismissed the petition after initially granting review and hearing oral arguments.[195] Justice Breyer, joined by Justice Stevens and Justice Souter, dissented from the dismissal. In his dissent, Breyer addressed the patentability of the process in *Lab. Corp.* and argued that the diagnostic process was nothing more than an unpatentable natural phenomenon.[196] (Rader's separate opinion in *Bilski* was in part a rebuttal to Breyer's opinion.) As with Rader's opinion, Breyer's opinion is not precedential.

The Supreme Court must also decide whether to grant review of *Prometheus Labs., Inc., v. Mayo Collaborative Servs.*, a September 2009 Federal Circuit Court of Appeals decision that applied the *Bilski* machine-or-transformation test to a patented medical diagnostic process. The patented process in *Prometheus* was a method for adjusting the dose of a drug based on the blood concentration of the drug's active metabolite after the drug is first given to a patient. The Federal Circuit determined that the process satisfied the transformation prong of the test because the first step of administering the drug results in "the various chemical and physical changes of the drug's metabolites that enable their concentrations to be determined."[197] If the Supreme Court decides to review this case, it will have a chance to directly address the patentability of diagnostic methods, which could bear on the patentability of association patent claims.

Given the importance of addressing existing patient access problems in a timely manner, the Committee's recommendations should be considered before this case is resolved. Even if *Bilski v. Kappos* has the effect of making association patent claims ineligible for patents, patents on isolated nucleic acid molecules will remain viable if the ACLU's clients do not prevail.

[191] *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006). The Court granted the writ of certiorari, heard oral arguments, and then dismissed the writ of certiorari as improvidently granted.
[192] Ibid.
[193] Ibid.
[194] Ibid.
[195] Ibid.
[196] Ibid.
[197] *Prometheus Labs., Inc., v. Mayo Collaborative Servs.,* Case No. 2008-1403 (Fed. Cir. Sept. 16, 2009).

The Nonobviousness Standard for Patents on Nucleic Acid Molecules

An invention cannot be patented if it would have been obvious to one of ordinary skill in the particular inventive field.[198] Patents were not designed to protect marginal improvements to technology that are obvious and to be expected.[199] For an invention to be patentable, then, it must be nonobvious. In judging nonobviousness, one compares the prior art—the prior knowledge and technology in a particular field—to the claimed invention, assesses the ordinary level of skill in the field, and then determines whether the invention represents an advance over the prior knowledge that is beyond the capacity of the ordinary artisan.[200]

With respect to patents claiming DNA molecules, the United States' test for nonobviousness has changed since two seminal cases in the mid-1990s, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) and *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995). In *Bell*, which is substantially similar to *Deuel*, the Federal Circuit considered an appeal from USPTO's rejection, on obviousness grounds, of patent applications claiming DNA molecules. The particular DNA molecules in question corresponded to insulin-like growth factor (IGF) proteins.[201] The prior art that the USPTO examiner had reviewed to make the obviousness determination consisted of two important pieces of information: the amino acid sequence of IGF proteins and a published laboratory procedure.[202] That laboratory procedure provided instructions for taking a protein sequence, creating a DNA probe from it using the genetic code, and then using that probe to obtain the protein's gene.[203] The patent applicants in *Bell* had used the known IGF amino acid sequence, created a DNA probe from it, and then used the probe to obtain the *IGF* gene.[204] As a final step, the patent applicants sequenced this gene, with that sequenced molecule claimed as an invention.[205] USPTO believed that based on the prior art, it would have been obvious to an ordinary molecular biologist to "find the nucleic acid when the amino acid sequence is known . . . ."[206]

The Federal Circuit Court of Appeals disagreed, holding the invention was nonobvious.[207] The court acknowledged that "one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene."[208] Nonetheless, because the genetic code is degenerate, with most amino acids corresponding to at least two different possible nucleotide sequences, the actual sequence of the gene could never be

[198] 35 U.S.C. § 103.
[199] Adelman, et al., op. cit.
[200] *Graham v. John Deere Co.*, 383 U.S. 1 (1966).
[201] *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).
[202] Ibid.
[203] Ibid.
[204] Ibid.
[205] Ibid. The court decision does not list the sequencing step, but this can be inferred from the patent applicant's possession of a sequence.
[206] Ibid.
[207] Ibid.
[208] Ibid.

predicted.[209] In essence, the court found that the inability of one to predict on paper the gene's sequence made the resulting molecule, when sequenced, nonobvious.

Arti Rai has critiqued the court's analysis, arguing that the focus of the inquiry should be on whether the laboratory procedures to obtain the gene would be obvious—not whether one could know beforehand, on paper, the gene's exact sequence.[210] However, this view was directly rejected by the Federal Circuit in *Deuel*. There, the Federal Circuit noted that even though it might have been "obvious to try" a standard method to obtain a gene from a protein, "'obvious to try' has long been held not to constitute obviousness."[211]

However, in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), the U.S. Supreme Court recently signaled a different approach, noting "the fact that a combination was obvious to try might show that it was obvious."[212] Although *KSR* did not involve a biotechnology invention, the Board of Patent Appeals and Interferences recently relied on it in deciding a case with facts similar to *Deuel*. In *Ex parte Kubin*, the Board rejected as obvious a DNA molecule whose sequence was derived from a known protein.[213] The Board reasoned that for an ordinary molecular biologist with a protein in hand, it would be obvious to isolate and sequence the corresponding DNA.[214] In other words, such sequencing would be "obvious to try." Although the Board asserted that *Deuel* was not relevant to the case, insofar as *Deuel* might be considered relevant, the Board found that the *KSR* decision overruled the *Deuel* principle that obvious to try does not constitute obviousness.[215]

The inventors appealed this decision, and on April 3, 2009, the Federal Circuit Court of Appeals decided *In re Kubin*, upholding the Board's decision that the claimed DNA molecule was obvious.[216] Based on this decision, a patent examiner can now find obviousness where the combination of certain elements was obvious—where, for example, it was obvious to combine knowledge of a protein's sequence and standard methods to find a gene based on a protein's sequence.

Prior to this Federal Circuit decision, USPTO had enacted "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in

[209] Ibid. As explained in a footnote to the decision, "A sequence of three nucleotides, called a codon, codes for each of the twenty natural amino acids. Since there are twenty amino acids and sixty-four possible codons, most amino acids are specified by more than one codon. This is referred to as 'degeneracy' in the genetic code."
[210] Rai, A.K. (1999). Intellectual property rights in biotechnology: Addressing new technology. *Wake Forest Law Review* 34:827-847; see also Cannon, B.C. (1994). Toward a clear standard of obviousness for biotechnology patents. *Cornell Law Review* 79:735-765 for a critique of Federal Circuit nonobviousness jurisprudence in biotechnology cases.
[211] *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995).
[212] The Supreme Court's principal holding in *KSR*, which did not involve a biotechnology invention, was to reaffirm the test of nonobviousness first laid out by the Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966).
[213] *Ex Parte Kubin & Goodwin*, No. 2007-0819, 2007 WL 2070495 (Bd.Pat.App. & Interf. May 31, 2007).
[214] Ibid.
[215] Ibid.
[216] *In re Kubin*, No. 2008-1184 (Fed. Cir. Apr. 3, 2009).

KSR International Co. v. Teleflex, Inc."[217] These guidelines signal that the patent office will consider obvious and unpatentable any applications that claim a DNA molecule derived from a known protein.[218] But even nucleic acid molecules derived through other means may be unpatentable after *KSR* and *In re Kubin*, according to Janis Fraser's assessment: "As a practical matter, if obviousness of a gene hinges on whether there was a known technique that could have been used to clone the gene, few if any gene inventions will pass muster."[219] In addition, existing patents on nucleic acids are now subject to *KSR's* and *In re Kubin's* obviousness standard and challenges against existing patents' validity will likely be brought.[220] Any party can challenge a patent's validity through a reexamination procedure.[221] In addition, a defendant in an infringement lawsuit can challenge the validity of a patent, and a party with standing can challenge a patent's validity through a declaratory judgment action.[222]

Although the Committee recognizes that *In re Kubin* may have weakened the ability of many patentees of nucleic acid molecules to enforce their patents, it is difficult to know for certain whether the genes claimed in older patents were discovered by means that would have been obvious to an ordinary person in the field at the time of their discovery (thereby making these older patents vulnerable to invalidation).[223] In addition, it is difficult to predict whether holders of patents on genes, regardless of the objective validity or invalidity of their patents, will conclude that their patents are invalid and stop enforcing them or whether they will operate under the belief that their patents are valid and continue to enforce them. Even if patent holders largely concluded their patent claims on genes were unenforceable, association patent claims would remain as a means of protecting genetic tests unless *Bilski v. Kappos* or the *Association for Molecular Pathology* case alters their patentability. Given the uncertainty surrounding the impact of recent decisions as well as pending and possible future cases, the Committee feels that its recommendations are the best way to address the problems and concerns identified in this report.

Clinicians are not Exempt from Liability for Infringing Biotechnology Patents

---

[217] Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*, Effective October 10, 2007, http://www.uspto.gov/web/offices/com/sol/og/2007/week45/patgide.htm.

[218] Ibid.

[219] Fraser, J.K. (2008). U.S. gene patents in legal limbo for now. Genetic Engineering and Biotechnology News, April, 1, http://www.genengnews.com/articles/chitem.aspx?aid=2422

[220] Stern, R.G., Bass, K.C., Wright, J.E., and M.J. Dowd. (2007). Living in a Post-KSR World, working paper created for The Sedona Conference on Patent Litigation VIII, http://64.237.99.107/media/pnc/1/media.121.pdf.

[221] The reexamination procedure can be found in Chapter 30 of United States Code Title 35. Some legal commentators have learned that the USPTO is working on establishing standards for determining when a reexamination challenge to an issued patent claiming a nucleic acid molecule raises "a substantial new question of patentability," as required by 35 U.S.C. § 303(a). It seems that challengers will not be able to merely cite *KSR* and ask for a re-review of the cited prior art. Stern, R.G., Bass, K.C., Wright, J.E., and M.J. Dowd. (2007). *Living in a Post-KSR World*, working paper created for The Sedona Conference on Patent Litigation VIII, http://64.237.99.107/media/pnc/1/media.121.pdf.

[222] The declaratory judgment action is made under 28 U.S.C. § 2201.

[223] The obviousness or nonobviousness of a discovery is evaluated by considering what would have been obvious at the time the invention was made. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

No existing law provides a safe harbor for clinicians who infringe patents when performing genetic tests. In 1996, U.S. patent law was amended to exempt medical practitioners from infringement liability for using patented medical or surgical techniques in medical practice.[224] Under the revised law, a court could decide that a physician had infringed a medical process patent but could not order that physician to pay damages or to stop using the technique. The liability protection was not extended to "the practice of a patented use of a composition of matter in violation of such patent, or . . . the practice of a process in violation of a biotechnology patent[,]" or "the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office) . . . ."[225]

In 2002, Representative Lynn Rivers (D-MI) introduced the Genomic Research and Diagnostic Accessibility Act of 2002, which included a provision to allow researchers and medical practitioners to use patented genes sequences for noncommercial research purposes and a provision to exempt clinicians performing genetic tests from patent infringement liability.[226] The bill did not become law.[227]

VII. BALANCING ACCESS AND INNOVATION: GUIDANCE FROM U.S. LAW AND POLICY, PREVIOUS POLICY STUDIES, AND OTHER LEGAL FRAMEWORKS

In considering what recommendations to make to the Secretary, the Committee reviewed three other broad areas. First, the Committee looked at existing technology transfer laws and policies, evaluating the mechanisms they provide for addressing patient access problems. The Committee also commissioned a review of licensing practice outcomes for DNA patents under two different policy frameworks, a framework created by the Patent and Trademark Amendments of 1980 (35 U.S.C. §§ 200-212, also known as the Bayh-Dole Act), which applies to academic institutions, and a framework created by the Stevenson-Wydler Technology Transfer Act of 1980, which applies to research conducted by NIH intramural scientists (i.e., Government employees) (see further discussion below). The Committee also reviewed the findings and recommendations of other groups that have looked at the effect of patents and licensing practices on patient access to genetic tests. Finally, the Committee considered the international patent and licensing landscape to see how other countries have tried to balance patent and licensing incentives with public access to genetic tests.

The Bayh-Dole Act

The Federal Government supports a significant amount of biomedical research. Prior to 1980, there was no Government-wide policy for the patenting and licensing of inventions made by the Government's grantees and contractors. The Government retained ownership of most inventions created with Federal funding, and very few of these were developed successfully into useful

[224] 35 U.S.C. § 287(c). This is sometimes referred to as the Frist-Ganske medical procedures exemption statute.
[225] 35 U.S.C. § 287(c).
[226] NIH Office of Legislative Policy and Analysis, http://olpa.od.nih.gov/legislation/107/pendinglegislation/9gene.asp.
[227] See http://www.govtrack.us/congress/bill.xpd?bill=h107-3967.

products or services. In 1980, the Federal Government held title to more than 28,000 patents, and fewer than 5 percent of these were licensed to industry for commercial development.[228]

The Bayh-Dole Act was signed into law in December of 1980 and became effective July 1, 1981. It was enacted to increase U.S. competitiveness and economic growth by promoting the transfer of inventions made with Government funding by Government grantees and contractors to the private sector for development into commercial products and services that would be beneficial and become available to the public. The Bayh-Dole Act allows Federal contractors and grantees to elect title to and patent their inventions that are conceived of or first actually reduced to practice in the performance of a Federal grant, contract, or cooperative agreement. The Act's policy and objectives include promoting "the commercialization and public availability of inventions made in the United States . . . ."[229]

With respect to any invention in which the contractor or grantee elects rights to an invention, the Federal Government is granted a "nonexclusive, nontransferable, irrevocable, paid-up license . . . ."[230] On November 1, 2000, the Bayh-Dole Act was amended to ensure that inventions made under it were used "without unduly encumbering future research and discovery."[231] Regulatory provisions associated with the enactment of the Bayh-Dole Act of 1980 stipulated the need for all grantees or contractors to report on the utilization of inventions that result from Federally funded research.[232]

To facilitate compliance with these legal requirements, the Interagency Edison (iEdison) tracking system and database was designed, developed, and implemented in 1995. This system facilitates and enables grantee and contractor organizations to directly input invention data as one means of fulfilling the reporting requirement. Since 1997, iEdison participation has grown to more than 1,300 registered grantee or contractor organizations supported by any of more than 29 Federal agency offices. Use of iEdison, however, is voluntary for inventions and patents developed under Federal funding agreements.

Under the Bayh-Dole Act, NIH may limit a grantee's right to elect title or NIH may elect title itself "in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives" of the Bayh-Dole Act.[233] If NIH believes such "exceptional circumstances" are involved, it must file a statement with the Secretary of Commerce justifying its determination of exceptional circumstances.[234] If the Secretary of Commerce agrees with the determination, the grantee can file an appeal with the U.S. Court of Federal Claims, and the determination of exceptional circumstances is to be held in abeyance until the appeal is resolved.[235]

---

[228] U.S. Government Accounting Office (GAO) Report to Congressional Committees. (1998). *Technology Transfer, Administration of the Bayh-Dole Act by Research Universities*. May 7.
[229] 35 U.S.C. § 200.
[230] 35 U.S.C. § 202(c)(4).
[231] 35 U.S.C. § 200.
[232] The regulatory provisions are found at 37 C.F.R. Part 401.
[233] 35 U.S.C. 202.
[234] Ibid.
[235] Ibid; 35 U.S.C. 203(b).

Arti Rai and Rebecca Eisenberg have argued that the requirement that agencies withhold patenting rights only "in exceptional circumstances" is too burdensome, potentially deterring NIH and other agencies from invoking the procedure when needed.[236] Rai and Eisenberg call for deleting this language from the statute, so that agencies such as NIH will have more discretion in controlling patenting rights.[237] NIH would use its discretion judiciously, they argue, because the agency recognizes the value of patenting in promoting commercial development of technology and would only withhold patenting rights from a grantee when it served the aims of the Bayh-Dole Act.[238] Rai and Eisenberg also recommend allowing research on the subject grant/award to proceed during the appeal of a determination.[239]

In addition to permitting the Government to elect title to an invention in exceptional circumstances, the Bayh-Dole Act permits a Federal agency to "march in" and secure broader rights from the holder of a patent that was funded by the Federal Government.[240] The four limited circumstances under which the Government can use its "march-in" rights are as follows: (1) when the grantee or contractor has not taken and is not expected to take within a reasonable time effective steps to achieve practical application of the subject inventions; (2) when such action is necessary to alleviate health or safety needs that are not reasonably satisfied by the contractor, assignee, or licensee; (3) when such action is necessary to meet requirements for public use that are not reasonably satisfied; and (4) when such action is necessary to provide preference for United States industry or "because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of such agreement."[241] In using its "march-in" authority, the Government can either require the grantee or contractor to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant(s) or the Government can grant such a license itself.[242]

Christopher Holman has proposed march-in as an option to remedy any potential problems that arise in patient access to genetic diagnostics.[243] However, Rai and Eisenberg have questioned the usefulness of the procedure as well, viewing it as just as burdensome as the administrative procedures involved in declaring exceptional circumstances.[244] In fact, as they explain, "the administrative obstacles are sufficiently cumbersome that NIH has never exercised these

[236] Rai, A.K., and R.S. Eisenberg. (2003). Bayh-Dole reform and the progress of biomedicine. *Law & Contemporary Problems* 66:289.
[237] Ibid.
[238] Ibid.
[239] Ibid.
[240] 35 U.S.C. § 203.
[241] 37 C.F.R. 401.14.
[242] 37 C.F.R. 401.14(j).
[243] Holman, C. H. Recent legislative proposals aimed at the perceived problem of gene patents. American Bar Association Biotechnology Section, available at http://www.abanet.org/scitech/biotech/pdfs/recent_legislative_chris_holman.pdf
[244] Rai, A.K., and R.S. Eisenberg, op. cit. To lessen the current administrative hurdles, Arti Rai and Rebecca Eisenberg called for changing "the requirement that march-in authority be held in abeyance pending exhaustion of all court appeals by the government contractor . . . ." These legal scholars argue that allowing agencies to proceed with march-in more expeditiously seems appropriate, given that march-in in some cases may be needed to alleviate health or safety needs.

rights."[245] Although NIH has considered three different march-in petitions, NIH in each case elected not to initiate march-in proceedings.[246]

In an article written in 1999, a former deputy director of the NIH Office of Technology Transfer, Barbara M. McGarey, and HHS Office of General Counsel attorney Annette C. Levey also characterize the march-in administrative process as burdensome.[247] In their view, if a situation arose where march-in was justified by a health care emergency, "the administrative process would likely not be expeditious enough to address the situation."[248]

In a report released by the Government Accountability Office (GAO) in July 2009, officials from the Department of Defense, Department of Energy, the National Aeronautics and Space Administration, and NIH also observe that the administrative processes when considering march-in are detailed and time-consuming and may make it difficult to initiate march-in.[249] However, "some officials also acknowledged that because the regulations are detailed, they ensure that appropriate and fair processes are followed during march-in proceedings."[250]

Given the administrative hurdles involved with march-in, McGarey and Levey suggest that alternative laws would be more effective if there is a public health need for an invention.[251] For instance, under 28 U.S.C. § 1498(a), the Government can practice an invention without a license if that practice is by or for the United States.[252] Despite the drawbacks of invoking the march-in provision, including the possibility that its frequent use would discourage licensing of Federally funded inventions, McGarey and Levey recognize its value as a "threat . . . to federal funding recipients to ensure appropriate commercialization of the inventions."[253]

Threatening march-in could be used to address the situation in which a holder of a patent on a Federally-funded invention refused to license or to grant a particular type of license. Assuming such refusal created one of the four conditions needed for march-in, the Government could credibly threaten march-in to induce licensing or actually march in to compel licensing. As such, although a Government threat to bring civil and criminal sanctions for anticompetitive behavior against a patent holder who refused to license is unlikely to be effective after the *Trinko* decision, a threat to bring march-in likely would be effective, but could only be used where the patented invention was developed with Federal funding.

NIH Policies Relating to Data Sharing

---

[245] Ibid.
[246] The three march petition determinations are available here: http://ott.od.nih.gov/policy/cellpro_marchin.pdf; http://www.ott.nih.gov/policy/March-In-Xalatan.pdf; http://www.ott.nih.gov/policy/March-in-norvir.pdf
[247] McGarey, B.M., Levey, A.C. (1999). Patents, products, and public health: an analysis of the CellPro march-in petition. *Berkeley Technology Law Journal* 14:1095-1116.
[248] Ibid., p. 1110.
[249] GAO. (2009). Information on the Government's Right to Assert Ownership Control over Federally Funded Inventions. GAO-09-742.
[250] Ibid.
[251] McGarey, B.M., Levey, A.C., op. cit.
[252] Ibid.
[253] Ibid., p. 1096.

The *NIH Principles and Guidelines on Sharing Biomedical Research Resources* encourages sharing of research tools developed by NIH-funded grant and contract recipients. [254] The document states that the goal of public benefit should guide those who are receiving NIH funds. The NIH also encourages grantees and contractors to comply with the 2005 guidance document *NIH Best Practices for the Licensing of Genomic Inventions* (see Box A). [255] For certain NIH-funded programs, compliance with the Best Practices policy is a term and condition of the grant or contract award. However, since the Best Practices encourage but do not force non-exclusivity, a grantee or contractor can still choose to license a genomic invention exclusively. In order to meet NIH programmatic and research goals, NIH has also determined that certain research findings, such as those involving full-length cDNA sequences from humans, rats, and mice, must be made available to the research community in named databases.

Box A: Excerpt from NIH Best Practices for the Licensing of Genomic Inventions

The optimal strategy to transfer and commercialize many genomic inventions is not always apparent at early stages of technology development. As an initial step in these instances, it may be prudent to protect the intellectual property rights to the invention. As definitive commercial pathways unfold, those embodiments of an invention requiring exclusive licensing as an incentive for commercial development of products or services can be distinguished from those that would best be disseminated nonexclusively in the marketplace.

Whenever possible, nonexclusive licensing should be pursued as a best practice. A nonexclusive licensing approach favors and facilitates making broad enabling technologies and research uses of inventions widely available and accessible to the scientific community. When a genomic invention represents a component part or background to a commercial development, nonexclusive freedom-to-operate licensing may provide an appropriate and sufficient complement to existing exclusive intellectual property rights.

In those cases where exclusive licensing is necessary to encourage research and development by private partners, best practices dictate that exclusive licenses should be appropriately tailored to ensure expeditious development of as many aspects of the technology as possible. Specific indications, fields of use, and territories should be limited to be commensurate with the abilities and commitment of licensees to bring the technology to market expeditiously.

For example, patent claims to gene sequences could be licensed exclusively in a limited field of use drawn to development of antisense molecules in therapeutic protocols. Independent of such exclusive consideration, the same intellectual property rights could be licensed nonexclusively for diagnostic testing or as a research probe to study gene expression under varying physiological conditions.

License agreements should be written with developmental milestones and benchmarks to ensure that the technology is fully developed by the licensee. The timely completion of milestones and benchmarks should be monitored and enforced. Best practices provide for modification or termination of licenses when progress toward commercialization is inadequate. Negotiated sublicensing terms and provisions optimally permit fair and appropriate participation of additional parties in the technology development process.

Funding recipients and the intramural technology transfer community may find these recommendations helpful in achieving the universal goal of ensuring that public health consequences are considered when negotiating licenses for genomic technologies.

[254] HHS. (1999). NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice. *Federal Register* 64(246). December 23. Notices. P. 72090, http://ott.od.nih.gov/pdfs/64FR72090.pdf.
[255] See http://ott.od.nih.gov/policy/genomic_invention.html.

PHS [The Public Health Service] encourages licensing policies and strategies that maximize access, as well as commercial and research utilization of the technology to benefit the public health. For this reason, PHS believes that it is important for funding recipients and the intramural technology transfer community to reserve in their license agreements the right to use the licensed technologies for their own research and educational uses, and to allow other institutions to do the same, consistent with the Research Tools Guidelines.

Available in full at: http://ott.od.nih.gov/policy/lic_gen.html.

NIH also encourages data sharing from genome-wide association studies, which are aimed at identifying common genetic factors that influence health and disease. Data sharing policies are also in place for the International HapMap Project, the goal of which is to compare the genetic sequences of different individuals from varying ancestries to identify chromosomal regions where genetic variants are shared. By making this information freely available, the project aims to help biomedical researchers find genes that play a role in disease and in drug responses.

In addition, the Genetic Association Information Network project, a public-private partnership between NIH and the private sector, also uses the approach set out in the *Best Practices* document. Collaborators have adopted an intellectual property policy that all of the data from this effort will be placed in a public database so that they can be shared with other investigators. This prevents third parties from taking inappropriate ownership and can reduce the overall cost of research by eliminating the need for others to duplicate the research to gain access to the same genomic data for data analysis and follow-on research.

Box B. Excerpt of NIH Policy for Sharing Data Obtained in NIH Supported or Conducted Genome-Wide Assocation Studies (GWAS)

V. Intellectual Property

It is the hope of the NIH that genotype-phenotype associations identified through NIH-supported and NIH-maintained GWAS datasets and their obvious implications will remain available to all investigators, unencumbered by intellectual property claims. The NIH discourages premature claims on pre-competitive information that may impede research, though it encourages patenting of technology suitable for subsequent private investment that may lead to the development of products that address public needs.

The NIH will provide approved GWAS data users with certain automated calculations (described under the Data Access section) as a component of the GWAS datasets distributed through the NIH GWAS data repository.

The NIH expects that NIH-supported genotype-phenotype data made available through the NIH GWAS data repository and all conclusions derived directly from them will remain freely available, without any licensing requirements, for uses such as, but not necessarily limited to, markers for developing assays and guides for identifying new potential targets for drugs, therapeutics, and diagnostics. The intent is to discourage the use of patents to prevent the use of or block access to any genotype-phenotype data developed with NIH support. The NIH encourages broad use of NIH-supported genotype-phenotype data that is consistent with a responsible approach to management of intellectual property derived from downstream discoveries, as outlined in the NIH's Best Practices for the Licensing of Genomic Inventions and its Research Tools Policy.

Available in full at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html

NIH's Technology Transfer Policies for Intramural Inventions

On October 21, 1980, two months before the Bayh-Dole Act was enacted, the Stevenson-Wydler Technology Transfer Act of 1980 was passed by Congress, and, in 1986, the Federal Technology Transfer Act (FTTA) of 1986 amended the Stevenson-Wydler Act. Similar to the purpose of the Bayh-Dole Act, FTTA's purpose is "[t]o promote United States technological innovation for the achievement of national economic, environmental, and social goals, and for other purposes."[256] FTTA authorizes Federal agencies to transfer Federally owned technology to the private sector for product development and authorizes the use of cooperative research and development agreements between Federal laboratories and non-Federal entities. Although there are similarities between the Bayh-Dole Act and FTTA, the latter has several distinct features, including the following: 1) a license may be granted only if the applicant has supplied a satisfactory plan for development and/or marketing of the invention;[257] 2) notices are published in the *Federal Register* of exclusive or partially exclusive licenses for Federally owned inventions that include the prospective licensee's name and a period of time for objection;[258] and, 3) the granting of exclusive, co-exclusive, or partially-exclusive licenses is contingent, not only upon notice in the Federal Register, but also upon a determination by the Federal agency that the grant of a license will not tend to substantially lessen competition.[259] The FTTA also limits the term and scope of exclusivity to not greater than reasonably necessary to provide the incentive for bringing the invention to practical application or otherwise promoting the invention's utilization by the public.[260]

NIH's intramural patent policy has been developed to be consistent with the Stevenson-Wydler Act and its amendments. The policy, applying to inventions developed in its intramural research programs, provides for the use of patents and other technology transfer mechanisms (such as license agreements, material transfer agreements, and research-only licenses) for biomedical technologies only when a patent facilitates the availability of the technology to the public for preventive, diagnostic, therapeutic, research, or other commercial uses. When commercialization and technology transfer can best be accomplished for intramural-made inventions without patent protection, such protection typically is not sought. NIH licensing policy for intramural-developed technologies seeks to promote the development of each technology for the broadest possible application and requires that commercial partners expeditiously develop the licensed technology. NIH only uses partially exclusive or exclusive licensing for its intramural-developed inventions when it is a reasonable and necessary incentive for the licensee to risk capital and resource expenditures to bring the invention to practical application or otherwise promote the invention's utilization.[261] If it is determined by NIH that a grant of an exclusive or partially exclusive license is necessary for further development of the technology, the terms and conditions of such exclusivity are narrowly tailored and are not greater than reasonably necessary.[262]

[256] 15 U.S.C. § 3701.
[257] 37 C.F.R. 404.5(a)(1).
[258] 37 C.F.R. 404.7(a)(1)(i).
[259] 37 C.F.R. 404.7(b)(1)(iii).
[260] 37 C.F.R. 404.7(C).
[261] 37 C.F.R. 404.7 (a)(1)(ii)(B).
[262] 37 C.F.R. 404.7(a)(1)(ii)(C).

To optimize the number of new products that will reach the market, NIH licenses its technology through nonexclusive licenses, exclusive licenses in narrowly defined fields of use, or exclusive licenses. Since 1990, the agency has also required that its licensed technology be made available for non-commercial research by for-profit, Government, and nonprofit researchers. Most NIH patent commercialization licenses are nonexclusive (80 percent), some are co-exclusive, and the few that are exclusive, in areas such as therapeutics or vaccines, are quite narrow (limited to a particular field of use, disease indication, or technology platform). As noted earlier, NIH grants exclusive licenses when it determines that they are a reasonable and necessary incentive for the licensee to risk capital and expenditures to bring the invention to practical application.[263]

Results of a Comparison of Licensing Under Two Statutory Frameworks

Since license exclusivity is often a topic of policy recommendations, a comparison of commercialization outcomes under different policy frameworks, one enabling more exclusivity in its licenses than the other, was undertaken.[264] The NIH OTT patents and licenses inventions from the NIH intramural research program under the Stephenson-Wydler Act. This Act favors nonexclusive licensing, requires a public notice period before granting licenses with exclusivity, and does not grant all field of use exclusive licenses.[265] The data for inventions developed by academic institutions were obtained in 2003 and 2004, and the data on NIH inventions extend through 2006.[266] For technical reasons, the data were not as comparable as had been anticipated. Also, there were no detailed product data for the academic institutions as those data were not part of the 2003 study. The differences in data may be due to the differing statutory frameworks and missions.

One of the preliminary findings of the study is that the differences in frequency and type of exclusivity in licenses from NIH are not markedly different from academic institutions. This was surprising given that the NIH OTT licensing framework under Stevenson-Wydler favors nonexclusive licensing relative to the academic institutions under Bayh-Dole. Another finding is that OTT maintains more never-licensed patents as a percentage of its total than do academic institutions operating under the Bayh-Dole Act (see Appendix XX). In addition, more DNA patents managed by academic institutions are licensed, overall, than those managed by the NIH OTT. This too could be explained by the differing statutory frameworks and missions or differences in the underlying research giving rise to different kinds of inventions.

The report also reaches the tentative conclusion that the elapsed time between patent filing, which in the biotechnology sector is generally a reasonable estimate of invention publication, and first revenue from license is somewhat longer under the NIH OTT practice framework than

[263] Driscoll, C., Director, Technology Transfer Office, National Human Genome Research Institute (NHGRI). Presentation to SACGHS. March 27, 2007.
[264] This study is still underway because the study authors plan to analyze additional data (76 licenses, including licenses for genes to detect pathogens such as HIV).
[265] http://www.ott.nih.gov/FAGs/#6 Accessed February 5, 2009
[266] Pressman L., et al. (2006). The licensing of DNA patents by US academic institutions: an empirical survey. *Nature Biotechnology* 24:31-39

under the academic practice framework. That is, patented inventions licensed by academic institutions reached the market sooner than those licensed by the NIH. This finding suggests that exclusivity may create development incentives, as the time from licensing to the introduction of a product on market appears shorter with exclusivity than without it.

There are many caveats to this finding that exclusively licensed technologies bear royalty income sooner on average than those that are licensed non-exclusively. First and foremost, the study design was limited in that it could only capture those technologies associated with a royalty-bearing license. The majority of diagnostic tests are laboratory-developed tests and are developed without patent protection or licenses. The study thus missed the large percentage of such genetic tests that are developed without a patent or license soon after a published genetic finding. Indeed in the case studies where there were (or are) exclusive licensees—for patents associated with breast cancer testing, hearing loss, HH, SCA, LQTS, and Canavan disease—in no case was the exclusive licensee first to market. In those cases, the patent was simply used to narrow or clear the market of tests that were already available.

Second, factors other than the differing licensing approach may explain why NIH inventions generate royalty payments later. For example, the study cites research showing that university inventors are more involved in the technology transfer process than are NIH inventors.[267] This greater involvement by university inventors could explain why their exclusively licensed inventions reach the market faster if exclusivity and inventor engagement are strongly correlated.

Third, the limited number of data points and wide variance between them created large standard deviations for the data on university-owned inventions. As a result, the difference between the two licensing approaches for university-owned patents has not been demonstrated to be statistically significant.

A separate finding from this study was that it was difficult to determine from examining issued patents whether rights associated with that patent came to be licensed for use in genetic testing. Neither a search algorithm nor scientists with biology expertise could reliably identify, when looking at patents alone, those patents whose rights had been licensed for use in a genetic test. This finding suggests that policy recommendations relating to patents and genetic tests should not focus on the patents themselves, but on their uses or their licensing.

In fact, none of the Committee's recommendations focus on the patents themselves; they instead concern the use of patents on genes—as defined in this report—for testing and research.

Nine Points to Consider in Licensing University Technology

[267] The study cites: Jansen, Dillon, "Where do the Leads for Licenses Come From" source Data from Six Institutions. Journal of the Association of University Technology Managers, vol. XI. p27 Ramakrishnan, Chen, Balakrishnan. Effective strategies for marketing biomedical inventions: Lessons learned from NIH license leads. Journal of Medical Marketing 5(4):342-352.

In 2007, a group of research universities and the Association of American Medical Colleges issued points to consider in managing intellectual property in the academic environment (see Box B). The Board of the Association of University Technology Managers has endorsed these points. Despite these guidelines, problems in patient access to patent-protected genetics have arisen, as described in this report.

Box C: "In the Public Interest: Nine Points to Consider in Licensing University Technology"

Point 1: Universities should reserve the right to practice licensed inventions and to allow other nonprofit and governmental organizations to do so.

Point 2: Exclusive licenses should be structured in a manner that encourages technology development and use.

Point 3: Strive to minimize the licensing of "future improvements."

Point 4: Universities should anticipate and help to manage technology transfer related conflicts of interest.

Point 5: Ensure broad access to research tools.

Point 6: Enforcement action should be carefully considered.

Point 7: Be mindful of export regulations.

Point 8: Be mindful of the implications of working with patent aggregators.

Point 9: Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world.

Source: Available in full at: http://www.autm.net/Nine_Points_to_Consider.htm

Previous Policy Studies

Four previous policy reports addressing the issue of patenting genes or biotechnology inventions merit attention, because they contain sections specific to genetic tests. These studies were conducted by the Nuffield Council on Bioethics (United Kingdom), the Australian Law Reform Commission (ALRC), the National Research Council (NRC) (United States), and the Organisation for Economic Co-Operation and Development (OECD).

Nuffield Council. The Nuffield Council on Bioethics, which is funded by two nonprofit charities and the U.K.'s Medical Research Council, issued *The Ethics of DNA Patenting* in 2002. The report urged raising the bar for obviousness and utility when granting DNA patents in the United Kingdom. The Council also advocated for limiting a patent's scope to identified uses:

> In our view, when patent examiners consider that a patent application that asserts rights over a naturally-occurring DNA sequence meets the criteria for patenting, the applicants could be required in some cases to disclose the specific uses to which they have demonstrated that the sequence can be put. The scope of protection would then be limited to these particular uses. In this way, at the very least, rights over entirely unrelated uses could not be subsequently asserted. The

scope of the monopoly awarded would, therefore, be commensurate with the actual contribution by the inventor.[268]

The Council also raised the possibility of compulsory licensing of diagnostic patents so that public health needs would be met.[269]

Australian Law Reform Commission. ALRC, an advisory body to the government, issued a major report addressing biotechnology and patents, devoting more attention to patents associated with genetic tests than any other government group. [270] With regard to Australian law and practices, the final 2004 ALRC report found "no clear evidence of any adverse impact, as yet, on access to medical genetic testing, the quality of such testing, or clinical research and development."[271] The report noted, however, that "some people in the Australian public health sector harbor genuine and serious concerns about the implications of gene patents. . . . There are arguments suggesting that the exclusive licensing of patents relating to medical genetic testing may have adverse consequences, depending on the behavior of licensees."[272] Among its recommendations, the Commission called for an experimental use exemption that would not be precluded by a commercial objective in undertaking the research.[273]

Organisation for Economic Co-operation and Development. OECD, a forum in which the governments of 30 countries work together to address the economic, social, and environmental challenges of globalization, issued *Guidelines for the Licensing of Genetic Inventions* in 2006.[274] These guidelines were developed in response to a 2002 workshop that investigated the impact of patents and licensing strategies of genetic inventions on access to information, products, and services for researchers, clinicians, and patients. Broadly speaking, the OECD guidelines support licensing practices that foster innovation, that promote dissemination of information and developments related to genetic inventions, and that encourage access to and use of genetic inventions for the improvement of human health.

In October 2003, the **Federal Trade Commission** issued a report, *To Promote Innovation: the Proper Balance of Competition and Patent Law and Policy*,[275] suggesting that broad patents may be having anti-competitive effects and blocking innovation in certain high-technology industries, such as computers and biotechnology. The report makes a number of recommendations aimed at restoring the balance between competition and patent policy and improving patent quality (e.g., by reducing the number of obvious patents). The report also recommends new mechanisms to make it less onerous to challenge invalid patents and new procedures to allow increased access to pending patents for the purpose of business planning and avoiding infringement.

---

[268] Nuffield Council on Bioethics. (2002). The ethics of patenting DNA. p. 65.
[269] Ibid., p. 48-56.
[270] ALRC. *Genes and Ingenuity: Gene Patenting and Human Health June 2004*. Australia: SOS Printing Group, http://www.austlii.edu.au/au/other/alrc/publications/reports/99/index.html.
[271] Ibid., p. 503, point 20.72.
[272] Ibid., p. 504, point 20.77.
[273] Ibid., List of Recommendations, 13-1
[274] See http://www.oecd.org/document/26/0,3343,en_2649_34537_34317658_1_1_1_1,00.html.
[275] Federal Trade Commission. (2003). *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*, http://www.ftc.gov/os/2003/10/innovationrpt.pdf .

National Research Council. As discussed earlier, NRC's 2006 report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*, was an immediate precursor to the current SACGHS study. The NRC committee commissioned three lines of inquiry, and staff conducted additional research. The committee drew on the DNA Patent Database for aggregate data on U.S. patents, worked with USPTO's Examining Group 1600, which reviews patent applications in the areas of biotechnology, pharmaceuticals, and organic chemistry, and commissioned a survey of scientists that explored research access to patented materials.[276] The NRC committee also performed its own analysis of specific cases, including some U.S.-European comparisons and the patents and licensing practices associated with genetic testing for breast cancer, Canavan disease, and Huntington disease. The Committee's review of the Huntington disease (HD) story indicates that researchers who discovered the HD gene sought to patent a method of using the gene for diagnosis because they "believed they might use the patent to control the testing process."[277] They also discussed using licenses associated with the patent on the isolated gene molecule to enforce testing and counseling protocols. However, to date, the patent assignee has not enforced its patent rights nor issued any licenses, and the HD test is available "from more than 50 academic and commercial laboratories in the United States."[278] The NRC report notes that the broad availability of the test allows verification of test results and that laboratories have collaborated to ensure the quality of testing:

> Once the HD gene was cloned, academic and commercial laboratories interested in testing took it upon themselves to develop the proper test methodology to ensure quality control. They shared test samples representing normal and variably sized expanded alleles in order to ascertain that all the laboratories were using the same techniques and getting comparable results. . . . Testing quality control by sending around test samples has been done periodically ever since.[279]

.

Most of the NRC report and recommendations focus on the impacts of intellectual property law and policies on research, but, as discussed earlier in this report, one of the recommendations calls for Congress to consider a limited statutory exemption from patent infringement liability for clinical verification testing:

> Recommendation 13: Owners of patents that control access to genomic- or proteomic-based diagnostic tests should establish procedures that provide for independent verification of test results. Congress should consider whether it is in the interest of the public's health

[276] Walsh, J.P., Cho, C., and W.M. Cohen. (2002). View from the bench: Patents and material transfers. *Science* 309**:**2002-2003. Walsh, J.P. Cho, C., and W.M. Cohen. Final Report to the National Academy of Sciences' Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions Patents, Material Transfers and Access to Research Inputs in Biomedical Research. September 20, 2005

[277] NRC. (2006). *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*. Washington, D.C.: National Academies Press. P. 66.

[278] Ibid. P.67.

[279] Ibid.

> to create an exemption to patent infringement liability to deal with situations where patent owners decline to allow independent verification of their tests.[280]

International Comparisons

As part of its study, SACGHS reviewed some of the patent law provisions of other countries to see whether they permit the patenting of genes and how these countries have responded to concerns about the effect of these patents on patient access to genetic tests.

According to an OECD report, all OECD countries allow patents on gene molecules:

> Although the appropriateness of granting patents on DNA and other nucleotide sequences continues to be publicly debated, the position of the official patent authorities in OECD countries has been more or less stable for some time. Assuming that a DNA sequence is novel (not previously publicly known or used in a public manner) and that the other criteria of patentability are also met (utility,inventiveness/non-obviousness), the substance of the DNA itself can be patented.To be precise, the claims concern not the sequence as abstract information, but a molecule which has the defined sequence and function.[281]

Moreover, a 1998 European Union Directive requires that all members of the European Union allow gene patenting in their national patent laws.[282] When Germany implemented the controlling EU directive into its national patent law, it added the limitation that a patent claiming a gene molecule would be limited to those industrial applications disclosed in the patent.[283] France has a similar provision in its patent law.[284] The effect of these provisions is that researchers do not need license rights to conduct research on a patented gene, and anyone whose discovers a new application of the gene may patent that application.[285] It is not clear, however, whether a gene patented for diagnostic application could be freely used by others for the kind of research described in this report—that is, using a gene in test runs of an improved genetic test. Interpretation of German and French law is beyond the expertise of the Committee; nor were any articles found discussing this narrow question.

According to German policy analyst Ingrid Schneider, in enacting these provisions, Germany and France

---

[280] NRC, 2006, op. cit., p. 18.
[281] Organization for Economic Co-operation and Development (2002). *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies*, http://www.oecd.org/dataoecd/42/21/2491084.pdf. P. 28.
[282] Council Directive 98/44, On the Legal Protection of Biotechnological Inventions, 1998 O.J. (L213) 13 (EC) at art. 5.2.
[283] Ann, C. (2006). Patents on human gene sequences in Germany: on bad lawmaking and ways to deal with it. *German Law Journal* 7:279-292. P. 286.
[284] Schneider, I. (2005). Civil society challenges biopatents in the EU. PropEur Newsletter. Summer 2005. No. 1 P. 3.
[285] Bryan, Erin. (2009). Gene protection: how much is too much? Comparing the scope of patent protection for gene sequences between the United States and Germany. *Journal of High Technology Law* 9: 52-65. Ann, C. (2006). Op. cit.

> argued that patents which were "too broad" in scope would "over-compensate" the inventor, would be counterproductive both scientifically and economically because of their potential to stifle the generation of new scientific knowledge, and would reduce the incentives for inventors working downstream in research and development.[286]

France has also passed a law permitting the government to issue compulsory licenses for patents protecting diagnostic methods, devices, and products.[287] Like France, Belgium, in implementing the EU directive, added provisions designed to mitigate the potential negative effects of biotechnological inventions on health care.[288] One provision is an expanded research exemption that makes clear that a patent holder's rights do not extend to research on or with the subject matter of the invention.[289] The scope of this research exemption is wider than that of other European countries, which permit only research on a patented invention.[290] The other Belgian provision allows for the government to grant non-exclusive compulsory licenses for public health reasons to patents protecting diagnostic methods, devices, and products.[291] According to Geertrui Van Overwalle and Esther van Zimmeren, this provision "was largely inspired by the restrictive licensing policy of the company Myriad Genetics, which refused to grant reasonable licenses to centres for genetic testing and hospitals."[292] These compulsory license provisions are broader than the U.S.'s march-in rights under the Bayh-Dole Act because they apply to all patents, not just patents secured after partial or full government funding of research.

Would Legal Changes Relating to Patents on Genes and Associations Violate TRIPS?

Countries that belong to the World Trade Organization (WTO), such as the United States, do not have unfettered discretion regarding their patent laws. Rather, they must afford at least as much patent protection as is required by the minimum standards enunciated in the WTO's Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS). Therefore, one question that arose during Committee discussions was whether legal changes affecting either the patent-eligibility of genes and associations or the enforceability of patents on genes and associations would be inconsistent with the U.S. obligations under TRIPS.

The Committee determined that there is no cause for concern as there is ample authority in the Agreement to support changes that promote access to, and research on, genetic testing. First, nations may elect to exclude from patentability diagnostic methods for the treatment of humans, plants, and animals other than microorganisms.[293] They can also exclude "inventions, the

[286] Schneider, I. Op. cit.
[287] Love, J.P. (2007). Recent examples of the use of compulsory licenses on patents. *Knowledge Ecology International.*
[288] Van Overwalle, G. and E. van Zimmermen. (2006). Reshaping Belgian patent law: the revision of the research exemption and the introduction of a compulsory license for public health. Chizaiken Forum 64:42-49.
[289] Ibid.
[290] Nuffield Council on Bioethics. (2002). The ethics of patenting DNA. p. 60.
[291] Van Overwalle, G. and E van Zimmermen. Op. cit.
[292] Ibid. P. 43.
[293] Article 27.3(a), TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.

prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality . . . including to protect human . . . health."[294] It thus appears that broader steps than those advocated here—namely the exclusion of genes or diagnoses based on genotype-phenotype associations from patent-eligibility—would be compatible with TRIPS.

Second, TRIPS permits members to define for themselves what constitutes an "invention."[295] Applying this principle, Argentina, Bolivia, Brazil, Columbia, Ecuador, Peru and Venezuela have chosen to classify isolated gene molecules as discoveries rather than inventions.[296] Similarly, should *Bilski* determine that simple associations are not patentable subject matter, the decision would not violate the TRIPS Agreement any more than the European Patent Convention's exclusion of programs for computers or diagnostic methods.[297]

Third, Article 30 of the TRIPS agreement provides:

> Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.[298]

Admittedly, this provision received a rather stingy interpretation in the only WTO case interpreting the Agreement in relation to a health care-related measure, *Canada–Patent Protection of Pharmaceutical Products*.[299] In that case, a dispute resolution panel held that the phrases in Article 30 are cumulative, requiring the respondent nation to justify an exception under each clause separately. In addition, the challenged measure was separately examined under Article 27 of the TRIPS Agreement, which requires members to make patents available "for any inventions . . . in all fields of technology."[300]

Canada-Pharmaceuticals was, however, decided by a WTO panel—the WTO analogue of a trial court. The Appellate Body (the WTO's "Supreme Court") has yet to address any of the exemption provisions found in the TRIPS Agreement.

More important, *Canada-Pharmaceuticals* was decided before the Doha Round of WTO negotiations. In that Round, a Ministerial Declaration emphasized that TRIPS must be

[294] Article 27.2, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.
[295] Heath, A. (2005). Preparing for the genetic revolution—the effect of gene patents on healthcare and research and the need for reform. Canterbury Law Review 11:59-?
[296] Ibid.
[297] European Patent Convention, art. 52(c) and (d), http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/ar52.html.
[298] Article 30, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.
[299] WT/DS114/R (March 17, 2000).
[300] Article 27.1, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.

interpreted "in a manner supportive of public health."[301] Furthermore, a separate Declaration on TRIPS and Public Health stated that

> the TRIPS Agreement does not and should not prevent members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health . . . .[302]

The Declaration continues, "In this connection, we reaffirm the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose."[303] As Alison Heath has suggested, the Declaration "may mean that a dispute regarding a gene patent measure aimed at improving access to healthcare will be approached with some leniency." As explained further below, the Committee's proposals are consistent with this approach to the Agreement.

Changes in the Enforceability of Gene Patents

A change in the enforceability of gene patents creates a limited exception. Since it does not interfere with the enforceability of these patents for therapeutics and furthers the legitimate interests of doctors and their patients, it appears to comply with Article 30 of the TRIPS Agreement, particularly when interpreted in light of the Doha Declaration.

Whether the provision must also comply with the technological neutrality principle of Article 27 is another issue. Now that the Ministerial Conference has confirmed the special treatment to be accorded to patents involving health care, a neutrality requirement no longer makes sense. But even if Article 27 continues to be applicable, *Canada-Pharmaceuticals* suggests that a provision could be framed in a way that passes muster. The law challenged in that case appeared to be nonneutral in that it was devised to permit generic drug companies to develop premarket clearance data during the patent period. Nonetheless, the panel reasoned that because any industry that was subject to pre-marketing approval could avail itself of the measure, Canada met the neutrality requirement of the Agreement.[304]

While this Committee is charged with the responsibility for making recommendations only with respect to gene patents, if Congress is concerned about meeting the requirements of Article 27, it could frame the exemption more broadly so that it provides relief to any industry experiencing the same problems that prompted this recommendation (for example, the impossibility of inventing around and the potential for deep patent thickets).[305]

---

[301] Doha Ministerial Declaration, WT/MIN(01)/DEC/1, 20 November 2001, paragraph 17, http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.htm.
[302] World Trade Organization. Declaration on the TRIPS agreement and public health. http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm
[303] Ibid.
[304] Id. at ¶ 7.102.
[305] Graeme Dinwoodie & Rochelle Dreyfuss, Diversifying Without Discriminating: Complying with the Mandates of the TRIPS Agreement, 13 MICH. TELECOMM'N & TECH'Y L. REV. 445 (2007).

Creation of a Statutory Research Exemption

Because most countries have broad research exemptions,[306] it is unlikely that any WTO member would challenge the research exemption proposed by the Committee as outside the scope of Article 30. Since the proposed exemption is, however, limited to gene patents, a challenge could be brought on technological neutrality grounds. But as explained above, such a challenge is not likely to succeed in the health care arena.

More importantly, Congress could avoid a challenge by casting the exemption broadly—for example, by reversing the Federal Circuit's decision in *Madey v. Duke* and restoring a general research exemption. Since the Committee was charged with the responsibility for making recommendations only with respect to gene patents, it could not propose such an exemption itself. But such an exemption has been urged by many commentators.[307] While there is empirical research suggesting that research is not hampered by the absence of a research defense, the findings suggest that scientists have persevered by developing a norm of ignoring patents.[308] An exemption that legitimized existing practice would promote the rule of law. Because patent holders' current revenue stream does not include payments for research uses, an exemption would not conflict or prejudice patent holder interests and thus would not, as Joshua Sarnoff and Henrik Holzapfel have concluded, violate Article 30.[309] And it would certainly be technologically neutral.

VIII. CONCLUSIONS

This Committee has a long-standing interest in recommending policies that will ensure the development of clinically useful genetic technologies, including genetic tests, and equitable access to these technologies. These concerns led the Committee to study the effect of patents on genetic test development and patient access. The Committee also studied the effect of patents on the quality of genetic tests because the reliability of a test is a fundamentally important component of any test. The conclusions and recommendations presented here reflect the consensus of the majority of the Committee. The views of three dissenting members are outlined in a statement at the end of this report.

---

[306] See the discussion under International Comparisons.

[307] Thomas, J.R. (2004). Scientific research and the experimental use privilege in patent law. Congressional Research Service Report for Congress .
ALSO: Katherine J. Strandburg, What Does the Public Get? Experimental Use and the Patent Bargain, 2004 Wis. L. Rev. 81; Maureen A. O'Rourke, Toward a Doctrine of Fair Use in Patent Law, 100 Colum. L. Rev. 1177 (2000); Janice M. Mueller, No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools, 76 Wash. L. Rev. 1 (2001); Rebecca S. Eisenberg, Patents and the Progress of Science: Exclusive Rights and Experimental Use, 56 U. Chi. L. Rev. 1017 (1989).

[308] See Rebecca S. Eisenberg, Patents and Data-Sharing in Public Science, 15 Indus. & Corp. Change 1013, 1018-19 (2006); John P. Walsh, Charlene Cho & Wesley M. Cohen, View from the Bench: Patents and Material Transfers, 309 Sci. 2002 (2005).

[309] See Holzaphel, H. and J. Sarnoff. (2008). A cross-Atlantic dialog on experimental use and research tools. Washington College of Law Research Paper No. 2008-13. P. 46-50. Musungu, S. (2007). Access to ART and other essential medicines in sub-Saharan Africa: Intellectual Property and Relevant Legislations. Report Commissioned by the United Nations Development Programme (UNDP) Regional Service Centre for Eastern and Southern

The Committee found that a near perfect storm is developing at the confluence of clinical practice and patent law. The cost of genetic analysis is decreasing dramatically, while knowledge about the genetic foundations for health, illness, and responsiveness to medicine is growing exponentially. There is now substantial potential for improving health using these new technologies. With genetic tests, physicians may be better able to identify their patients' genetic predispositions and help patients take steps to avoid—or at least minimize—the effects of their vulnerabilities. Genetic information can also be used by pharmaceutical and biotech companies to develop therapeutics targeted to subpopulations with specific genetic variations, while physicians can use this information to identify those patients who will benefit from these targeted therapeutics.

Trends in patent law appear, however, to pose serious obstacles to the promise of these developments. Patenting has moved upstream; instead of covering only commercial products, patents can now control foundational research discoveries, claiming the purified form of genes. Fragmented ownership of these patents on genes by multiple competing entities substantially threatens clinical and research use. While new technologies enable simultaneous evaluation of multiple genes through multiplex testing, parallel sequencing, and whole-genome sequencing, fragmented ownership may create a host of problems such as patent thickets, blocking patents, high transaction costs, royalty stacking, and holdouts. Some of these problems have already come to light. Indeed, already, some laboratories using multiplex tests have chosen not to report to patients or clinicians the results for certain patent-protected genes for fear of being sued.[310] In short, the evidence indicates that patents have already limited the potential of these tests.

U.S. law has decreasing capacity to mitigate these problems. Unlike many other countries, the United States does not have compulsory licensing rules to deal with problems of blocking or holdouts. In addition, its research exemption is nominal; it essentially shields from infringement liability only research required to develop information needed for FDA approval. And antitrust law does not set limits on a patentee's power to refuse to sell or license its technologies.

In other fields of technology, these shortcomings in U.S. law have not caused overwhelming problems because patents in other fields can be invented around. But gene and association patents often claim (or come close to claiming) fundamental principles of nature; therefore, it is frequently not possible to invent around these patents to produce materials of equivalent diagnostic and research value. In fact, for all conditions that are caused by a single mutation, inventing around the patented mutation to create a genetic test is very difficult if not impossible. Even when inventing around is possible, it is inadvisable. For example, in the case of single-gene conditions, although it is sometimes possible to design around a patent on a gene or association by using an unpatented marker that is linked to the gene through the phenomenon of linkage disequilibrium, the vast majority of single-gene diseases do not demonstrate linkage disequilibrium. Therefore, in the majority of cases, this strategy for avoiding patent infringement

[310] While it may be that not reporting test results prevents the patent holder from becoming aware of the use of patent-protected genes or probe molecules, performance of the test is still infringement so long as the probe molecules used in the test are claimed by the patent or equivalent to what the patent claims.

in clinical testing is unavailable. Furthermore, even when an associated marker is available and unpatented, using the associated marker for testing will, due to inherent genetic constraints, necessarily lead to more false positives and false negatives. Because these false positives and false negatives can only discovered by testing for the gene itself, clinicians who relied on a marker test alone would make diagnostic errors unbeknownst to them that could cause significant management consequences. Thus, using an associated marker to invent around a patented gene does not produce a genetic test of equivalent value to direct analysis of the gene in question.

Because of these issues, U.S. patent law not only threatens medical progress, it may also drive valuable genetic research to countries with a more hospitable legal climate. For example, Belgium has a broad research exemption that makes research on or with isolated gene molecules exempt from infringement.

If patents on genes were necessary to stimulate research and genetic test development, it might be necessary to tolerate the social harms identified in this report. However, patents do not appear to be necessary to stimulate research and genetic test development; most troubling in the diagnostic realm, patent rights have been used to clear the market after broad testing was developed by multiple entities. As demonstrated by the research in this report, researchers have strong non-patent incentives to engage in research on the genetic basis of diseases: academic research is curiosity- and reputation-driven. Moreover, the Federal Government and nonprofits fund much of this research. Similarly, laboratories have sufficient non-patent incentives to develop genetic tests: clinical need and demand drive development, and development costs are minimal. Even when development costs are more substantial—as they are for development of an approved test kit—a lack of exclusive rights has not prevented multiple companies from investing in test development.

Nor are patents needed to encourage disclosure. In academia and medicine, disclosure of discoveries is encouraged and rewarded, and trade secrecy is not a feasible option.

Analysis of Potential Approaches to Addressing Problems in Test Development and Patient Access

The Committee evaluated a variety of potential approaches to addressing the identified problems in genetic test development and patient access, seeking a solution that was complete, narrowly tailored, and that could be accomplished expeditiously. A number of considered approaches failed to meet at least one of these criteria.

For example, the Committee considered whether to recommend that Government use its march-in rights under the Bayh-Dole Act to address existing problems. Under this Act, an agency that funded genetic research that resulted in a patented gene or association could require the patent holder to grant non-exclusive licenses to other laboratories and companies or could grant these licenses itself. However, the procedures involved in marching in are complex and make pursuit of this option to obtain rights inefficient. While commentators have proposed changes to the Bayh-Dole Act to lessen the administrative burdens involved in marching in, the Committee

chose not to recommend these changes because, even if march-in were more efficient for each individual case, pursuing separate march-in proceedings for each Federally-funded patented gene or association that is exclusively licensed would be a time-consuming and burdensome process. Moreover, because march-in can only be used against patents on inventions that resulted from Federal funding, it could not remedy problems caused by patents on inventions that were not Federally funded, including, among others, some of the patents that protect molecules and methods used for breast cancer genetic testing and a patent that protects molecules and methods used for testing for a hearing loss gene.[311] Thus, this approach would not be expeditious and would fail to address all problems.

Similarly, it has been suggested that existing problems could be addressed by strengthening NIH guidelines relating to technology transfer. But once again, such changes would affect only Federally-funded inventions. While there are also non-NIH guidelines that seek to promote non-exclusive licensing, the Committee chose not to recommend stronger promotion of these guidelines as its principal recommendation since such non-binding guidelines have existed for some time and not prevented the identified problems from occurring. Moreover, the Secretary has no authority to enforce these guidelines.

The Committee likewise rejected recommending a ban on patenting genes or associations. A bill that would have established such a ban was, in fact, introduced by Congressman Xavier Becerra in 2007. The bill called for amending patent law so that "no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies."[312] The legal changes called for in proposed legislation, however, would not have applied to a patent issued before the bill's enactment.[313] Thus, it would not have solved the problems identified in this report, which involve existing patents. While a ban that was both retroactive and prospective would solve these problems by eliminating exclusive rights to genetic testing, it would also eliminate exclusive rights to therapeutic uses of genes. The importance of exclusive rights to genes for the development of therapeutics was not studied by the Committee, so it seemed prudent not to alter the availability of these rights without knowing whether it would have harmful effects for therapeutic development. The Committee instead wanted an approach that was narrowly tailored to improve genetic test development and patient access without affecting patent rights in other areas.

The Committee also rejected an approach targeted only at sole-source providers. This approach would have involved a legal change that gave the Government the authority to compel licensing or grant a license itself if a sole source provider refused to license voluntarily. A shortcoming of this approach is that testing providers might satisfy the requirement of licensing by only licensing to one other laboratory, and a duopoly would not guarantee a solution to patient access problems.

[311] See Myriad patents 5,693,473; 5,709,999; 5,837,492; and 6,033,857. Patent 5,998,147 claims a purified nucleic acid molecule whose sequence corresponds to the mutated form of the connexin 26 gene, which accounts for up to half of all non-syndromic recessive hearing loss cases.
[312] H.R. 977, 110th Cong. § 2 (2007).
[313] Ibid.

The Potential Impact of Recent and Pending Legal Decisions

During the time this report was being finalized, a number of new cases relating to patents on genes and/or patents on associations were reviewed to determine whether they would eliminate existing problems in test development and patient access. One potentially salutary legal development is a recent change in the standard for determining whether an isolated nucleic acid molecule is nonobvious.[314] Although existing patents on genes can now be challenged on obviousness grounds under the revised standard established in *In re Kubin*, it is far from certain whether all or most of these patents will be vulnerable to invalidation. Even if they are, the process of challenging each of these patents separately would be extremely time-consuming and costly.

A pending case goes further than *In re Kubin* by challenging the patentability of genes and associations. That case, *Association for Molecular Pathology, et al. v. United States Patent and Trademark*, gives the federal courts the first opportunity to directly address whether the isolated gene molecules and associations claimed in some patents are unpatentable products or principles of nature; the case particularly concerns patents protecting breast cancer genetic testing. Although this case stands to solve some of the problems in access to breast cancer genetic testing, its outcome is uncertain. Furthermore, even if the plaintiffs prevail, this would not lead to the automatic invalidation of all existing patents on genes and associations.[315] Depending on how the decision is framed, there may be a continuing need to challenge patenting strategies.

Another case, *Bilski v. Kappos*, anticipated to be decided by the U.S. Supreme Court by June 2010, may also have implications for the patentability of gene-disease associations, although not patents on genes. The Court is considering as well a petition to review *Prometheus Labs., Inc., v. Mayo Collaborative Servs.,* a case that concerned the patentability of a diagnostic method. If the Supreme Court decides to review this case, its decision may bear upon the patentability of associations.

In *eBay v. MercExchange,* the Supreme Court also limited the strength of patent protection by giving courts discretion over awards of injunctive relief and suggesting that injunctions can be denied when there is an important public interest at stake. There is, however, substantial uncertainty regarding how this case will be interpreted. Although permitting infringement of certain inventions might serve a public interest in free availability of those inventions, it is unlikely that courts will generally deny injunctive relief as this would diminish patent incentives for invention. Courts may instead award permanent injunctions but suspend the application of the award in order to give defendants enough time to invent around.[316] While this approach may solve holdout and thicket problems in the software and business sectors, where it is possible to

[314] *In re Kubin*, No. 2008-1184 (Fed. Cir. Apr. 3, 2009).

[315] As the attorney for the plaintiffs explained in a recent interview, "Success in this case will encourage new lawsuits regarding any or all of those [existing] patents [on genes]. Theoretically, the facts in each instance are sufficiently different so that there would be no across-the-board invalidation of the patents. Each case would be separate." Albainy-Jenei, S. (2009). Bulletproof: Interview with ACLU attorney Chris Hansen over gene patents. Patent Baristas web site, November 12, 2009. http://www.patentbaristas.com/archives/2009/11/12/bulletproof-interview-with-aclu-attorney-chris-hansen-over-gene-patents/

[316] See, for example, *i4i L.P. v. Microsoft Corp.,* Fed. Cir., No. 2009-1504, 12/22/09.

invent around, it would not help those who wish to use genetic information that cannot be invented around.

Rather than wait on cases that in the end may not fully address identified problems, the Committee recommended actions that address these problems directly and expeditiously.

Possible Health Care Reform

As this report was being finalized, Congress was debating changes in health care insurance law. It remains uncertain whether health care insurance reforms will be enacted and, if they are, what form they would take. However, none of the changes under consideration appear to address the problems identified in this report. Nor is it clear how changes affecting health insurers could solve the problem caused by a sole provider's decision not to accept a particular insurance. To solve this access problem, a legal change would have to require the sole provider to accept all insurers. But even if this legal change were made, it would not solve other problems associated with patent-protected sole providers: namely, the inability of patients to obtain second-opinion testing from independent providers and concerns about the quality of tests. Finally, this legal change also would not address the barrier patent thickets present to the development of new testing technologies, such as multiplex testing.

Recommended Changes to Improve Test Development and Patient Access

The Committee identified two narrowly tailored statutory changes that, if enacted, would solve the identified problems in an expeditious manner.

First Recommended Statutory Change

One of the principal legal changes that the Committee proposes is an exemption from liability for anyone who infringes a patent on a gene while making, using, ordering, offering for sale, or selling a genetic test for patient care purposes. If this change is enacted, tests that under the current system are offered by only an exclusive rights holder could be offered by multiple providers. One can reasonably expect that multiple laboratories and companies would pursue development of these tests, given that when there are non-exclusive rights and free market conditions, multiple laboratories actively develop needed tests. For example, although patents protect genes involved in Lynch syndrome, the patents have not been enforced, and at least 15 different U.S. laboratories have developed genetic testing for this condition.[317] Similarly, exclusive rights to testing for Huntington disease are not being enforced, and multiple laboratories have developed genetic tests for that disease. The evidence thus suggests that free market conditions, unencumbered by patent-enabled exclusivity, are conducive to the development of genetic tests. Where exclusivity does not prevail, as in the cases of CF, Huntington disease, Lynch syndrome and myriad others, a thriving market appears in which laboratories—both public and private—compete on the basis of service and quality. Indeed, it is

[317] As of December 2009, GeneTests.org list 14 laboratories that perform this test; the case study on breast and colon cancer indicates that Myriad Genetics also offers this test.

when patents are used in the diagnostic arena to limit access and suppress free market conditions that the problems documented in this report arise.

By restoring free market conditions, the recommended statutory change would eliminate patient access problems. If multiple providers can offer tests that under the current system are offered by only a single exclusive-rights holder, patients are much more likely to find that at least one of the providers accepts their particular insurance. The existence of multiple providers for a particular test would also permit second-opinion testing and the sharing of samples to ensure the quality of testing. In addition, the recommended statutory change would permit the wider development of new testing technologies, such as multiplex tests. Developers who wish to create these tests will no longer face the difficult prospect of acquiring rights to multiple patents.

The proposed statutory change does not eliminate gene patents. Rather, it is narrowly tailored and applies only to diagnostic use of gene patents in the context of patient care. Privately funded genetic research, which is supplemental to government-funded genetic research, is often driven by the desire to develop a therapeutic, whether in the form of a drug or a gene-based therapeutic. Because patents on genes would remain available and enforceable for therapeutic uses with this statutory change, the prospect of a patent on a gene or on a therapeutic would still serve to stimulate private investment in basic genetic research. The narrow tailoring of the exemption also leaves undisturbed the ability to enforce patent rights to test kits, platform technologies, and methods of genetic analysis that do not rely on specific patent claims on human genes.

Exemption is Advisable Even if FDA Begins to Regulate Laboratory-developed Tests

Under the current system for oversight of genetic tests, laboratory-developed tests are not subject to FDA pre-market review, and thus the costs associated with an existing laboratory launching a laboratory-developed test are relatively low—roughly $8,000 to $10,000 for each gene tested. There have been increasing calls in recent years, however, for the FDA to increase regulation of laboratory-developed genetic tests.[318] In fact, this Committee has recommended that the FDA "address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests."[319] The Committee elaborated that the FDA should "optimize the time and cost of review without compromising the quality of assessment."[320] In other words, the review process should be sufficient to ensure the quality of the test without being so daunting that companies are discouraged from pursuing test development.

If in the future the FDA does take a larger role in the oversight of laboratory-developed genetic tests, the cost of developing an approved laboratory-developed genetic testing service may become more substantial, similar to the costs of developing an FDA-approved test kit. Whether academic laboratories will have sufficient resources to pursue such FDA approval is unclear. However, even if these laboratories cannot pursue FDA approval, the case study on cystic

[318] Kuehn, B. (2009). Growing calls in United States, Europe to improve regulation of genetic testing. *Journal of the American Medical Association* 302:1405-1408.
[319] SACGHS. (2008). U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services.
[320] Ibid.

fibrosis reveals that multiple entities are willing to pursue FDA approval of a genetic test—in that case a test kit—even though they lacked exclusive rights to test kit development. Therefore, at least for common conditions, multiple companies lacking exclusive rights likely will still invest in creating laboratory-developed testing services even if they have to obtain FDA approval. As such, the expectation of increased FDA oversight of laboratory-developed tests is not a reason to reject the many benefits presented by the exemption the Committee proposes. This exemption will lead to wider test development, not less test development, even if the FDA takes on oversight of laboratory-developed tests.

Second Recommended Statutory Change

The second principal legal change that the Committee proposes is the creation of an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research. This change—which, like the first recommendation, does not eliminate gene patents—is narrowly focused on permitting scientists to use genes in research efforts to develop new genetic tests and therapeutics; research on genes could also yield insights that lead to the development of new methods of prognosis and risk assessment. While it is not clear whether patent-rights holders have consistently sought to enforce their patent rights to prevent such research, even if patents have not been enforced against such research, an exemption from liability would provide complete assurance to scientists that such research is permissible. Finally, in the Committee's view a research exemption is entirely consistent with the aim and intent of the patent system, i.e., the promotion of the progress of useful arts.

Since the Committee's focus is strictly on addressing potential impediments to the development of and patient access to genetic tests, it did not evaluate the appropriateness of, nor recommend, a general research exemption in all areas of science. However, if Congress is concerned that a research exemption limited to patents on genes violates Article 27 of the WTO's Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), which requires technological neutrality, Congress could broaden the exemption from infringement for research on all patents or research involving all upstream patents.

The Committee's narrow focus on nucleic-acid-based genetic tests limits its recommendations in other ways as well. Specifically, the Committee's recommendations do not extend to patents on proteins—a subject that the Committee was not charged to study. These patents were excluded from the scope of the study because most genetic tests detect genetic sequences rather than proteins. However, if there are any concerns about the effects of protein patents on the development of and access to protein-based genetic tests, other groups may wish to undertake a study of this issue and may well find that analogous recommendations are appropriate.

Finally, the Committee is cognizant of the fact that patent and licensing practices should not be changed lightly or without sufficient cause. Indeed, in the realm of commodities or consumer electronics it may well be that dramatic harms and a profound lack of benefit should be required to compel any recommendation for change. But genetic tests affect patients' lives and health. Thus, the current system's net negative effects on test development and patient access to these tests argue strongly for the narrowly tailored changes that are proposed.

IX. RECOMMENDATIONS

Recommendation 1: Support the Creation of Exemptions from Infringement Liability

The Secretary of Health and Human Services should support and work with the Secretary of Commerce to promote the following statutory changes:

A. *The creation of an exemption from liability for infringement of patent claims on genes for anyone making, using, ordering, offering for sale, or selling a test developed under the patent for patient care purposes.*

B. *The creation of an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research.*

The Committee believes the changes described in Recommendation #1 offer the most expeditious and straightforward way of addressing the identified problems and promoting patient access to emerging genetic advances.

If enacted, the first recommended statutory change would allow service providers to offer gene-based diagnostic testing unimpeded by fear of infringing patent claims on genes and would apply to both commercial and non-commercial laboratories. It would also allow test kit makers to make, offer for sale, and sell genetic test kits without the need to obtain licenses to any patented nucleic acid molecules included in kits. The ability of multiple providers to offer test that currently are available from only one source should solve the patient access problems identified in this report. With more providers, a patient will have a better chance of finding at least one who accepts their health insurance. The change will also permit second-opinion testing, the development of new forms of existing tests, the development of multiplex tests, and the sharing of samples to ensure the quality of testing. This narrowly tailored exemption permits the holders of patents on genes to continue to enforce their exclusive rights to therapeutic uses of the claimed molecules, thereby preserving the incentive such patents create for the development of therapeutics. Moreover, by preserving the right to patent genes and enforce those patents for therapeutic applications, this exemption maintains the strong incentive patents create for privately funded basic genetic research, which is often ultimately driven by the hope of developing a therapeutic.

The second recommended statutory change—providing an exemption from infringement for research on or with genes—is designed to permit research that can generate insights into disease, genetic tests, and therapeutics.

In addition to these formal recommendations, the Committee also urges the Secretary to use current authority to discourage the seeking, the granting, and the invoking of any patents on simple associations between a genotype and a phenotype. Association patent claims threaten the availability of existing genetic tests and are an anticipated barrier to the development of testing innovations, such as microarrays and whole genome sequencing.

The steps called for in Recommendations #2 and #3 below can likely be accomplished more quickly than the statutory changes required in Recommendation 1, given that, even when there is political support for a particular legal change, law-making can proceed at a slow pace. Nonetheless, the Committee regards the statutory changes as the most effective means of addressing the identified problems.

The actions called for in Recommendations #4 through #6 will foster progress, regardless of whether Congress enacts the proposed statutory changes.

Recommendation 2: Promote Adherence to Norms Designed to Ensure Access

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will increase adherence to current guidelines that promote non-exclusive licensing of diagnostic genetic/genomic technologies.

The Secretary should convene stakeholders—for example, industry, academic institutions, researchers, patients—to develop a code of conduct that will further broad access to such technologies.

The Committee supports guidelines that encourage broad licensing and broad access to diagnostic genetic/genomic tests.[321]

NIH's *Best Practices for the Licensing of Genomic Inventions* and the *OECD Guidelines for Licensing of Genetic Inventions* discourage exclusive licensing for genetic/genomic inventions. Points Two and Nine of the Nine Points to Consider in Licensing University Technology, including their explanatory text, are also relevant for genetic tests. In particular, the explanatory text under Point Two recognizes that "licenses should not hinder clinical research, professional education and training, use by public health authorities, independent validation of test results or quality verification and/or control."

In identifying mechanisms that will promote adherence to the guidelines, the Department may need to determine the scope of its authority under existing statutes. For example, the Department may have to clarify whether the Bayh-Dole Act gives agencies authority to influence how grantees license patented inventions.

If it is determined that the HHS has this authority, one way the HHS Secretary could promote adherence to the licensing guidelines would be to direct NIH to make compliance with them an important consideration in future grants awards.

[321] Such guidelines include NIH's Best Practices for the Licensing of Genomic Inventions; the Organisation for Economic Co-Operation and Development's (OECD's) Guidelines for Licensing of Genetic Inventions; the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-wide Association Studies; and In the Public Interest: Nine Points to Consider in Licensing University Technology.

Alternatively, the Secretary could promulgate regulations that enable the Department's agencies to limit the ability of grantees to exclusively license inventions resulting from Government funding when they are licensed for the genetic diagnostic field of use. Exceptions could be considered if a grantee can show that an exclusive license is more appropriate in a particular case—for example, because of the high costs of developing the test.

Recommendation 3: Enhance Transparency in Licensing

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will make readily available to the public the following information from licenses executed by patent holders: the type of license and the field of use for which rights were granted.[322]

As a means to enhance public access to information about the licensing of patents related to gene-based diagnostics, the Secretary should also direct NIH to amend its *Best Practices for the Licensing of Genomic Inventions* to encourage licensors and licensees to include in their license contracts a provision that allows each party to disclose non-financial information about its licenses (particularly such factors as type of license, field of use, and scope) in order to encourage next-generation innovation.

The case studies discovered that it is often difficult for parties to obtain information on the scope of licenses. Such license information could reveal whether any rights to use the patented invention remain available. Test developers need such information to effectively plan what innovations to pursue. For example, if a license reveals that a particular gene has been exclusively licensed in all fields and may not be sublicensed, a developer would then know not to pursue innovations that require use of that gene. The recommended actions would make relevant licensing information more readily available.

Recommendation 4: Establish an Advisory Body on the Health Impact of Gene Patenting and Licensing Practices

The Secretary should establish an advisory body to provide ongoing advice about the health impact of gene patenting and licensing practices. The advisory body also could provide input on the implementation of any future policy changes, including the other proposed recommendations in this report.

This advisory body would be available to receive information about patient access to genetic tests from the public and medical community. The body could review new data collected on patient access and identify whether problems are occurring and if so to what extent.

One of the advisory body's missions would also be to recommend what additional information should be systematically collected through iEdison so that iEdison can be used to determine whether grantees are complying with the guidelines mentioned in recommendation #2.

[322] Because of the public importance of this information, we advocate that it not be regarded as suitable for protection as trade secrets.

The advisory body could also explore whether approaches to addressing patent thickets, including patent pools, clearinghouses, and cross-licensing agreements, could facilitate the development of multiplex tests or whole genome sequencing.

The advisory body should consist of Federal employees and outside experts from a broad array of areas; for example, the body could be made up of clinical geneticists, patent law experts, researchers, consumers, representatives from the diagnostic kit industry, commercial laboratory directors, technology transfer professionals, laboratorians, and Federal employees from USPTO and NIH.

Such an advisory body could be established within a relevant existing committee.

Recommendation 5: Provide Needed Expertise to USPTO

The Secretary should work with the Secretary of Commerce to ensure that the USPTO is kept apprised of scientific and technological developments related to genetic testing and technology.

The Committee believes experts in the field could help USPTO in its development of guidelines on determinations of such matters as nonobviousness and subject matter eligibility, particularly the patent-eligibility of methods that rely on the association between a genotype and phenotype.

Recommendation 6: Ensure Equal Access to Clinically Useful Genetic Tests

Given that genetic tests will be increasingly incorporated into medical care, the Secretary should ensure that those tests shown to have clinical utility are equitably available and accessible to patients.

Such uniformity in coverage would ensure that all insured patients, regardless of geographic location or economic status, obtain access to clinically useful genetic tests.

Our advocacy for equal access here is part of this Committee's long-standing concern about ensuring equity in the provision of genetically related tests and services. Earlier reports and recommendations have called attention to the importance of equitable access to genetic testing.

X. APPENDICES

Appendix A: Compendium of Case Studies Prepared for SACGHS by the Duke University Center for Genome Ethics Law & Policy

[To be added]

Appendix B: Preliminary Findings from a Population Level Study of DNA Patents by Lori Pressman, Mark Rohrbaugh, and Stephen Finley

[To be added]

Appendix C: List of Public Commenters

[To be added]

STATEMENT OF DISSENT FROM MS. ASPINALL, DR. BILLINGS, AND MS. WALCOFF

We respectfully disagree with conclusions and recommendations of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) Gene Patenting report based on our assessment of the evidence available, knowledge of the diagnostics industry and understanding of academic research collaborations. In our current health care system, patients routinely face unequal access to medical care, including diagnostic tests. Consequently, it is our position that statutorily modifying the gene patents system, including the creation of exemptions from liability for infringement upon such patents as defined in this report and proposed in the recommendations, would be more harmful than helpful to patient access and to the quality of innovative genetic diagnostics.

The basis of our position is recognition that there are a variety of financial and scientific decisions made by both government and private stakeholders throughout our health care system that impact patient access to genetic tests. We recognize the importance of supporting and encouraging discovery and, most importantly, translating those genetic discoveries into new tools to improve patient treatment and outcomes.

The patent system, although debatably imperfect, offers those who invest in developing discoveries a value for the investment. We believe that facts and findings cited in this report and in other reliable scientific literature support our view that the recommended change to the patent enforcement statute and the Bayh-Dole Act would have significant negative consequences. Many discoveries, in academic institutions or otherwise, may not be pursued or developed. Notably, the increasing complexity of development and clinical testing for genetic tests and higher evidentiary standards and regulatory hurdles such tests must meet require increasing levels of investment (measured in millions or tens of millions).

Notwithstanding our position that the recommendations regarding the statutory changes to the patent system would not ameliorate the patient access concerns this Committee has identified, we do acknowledge and appreciate the importance of patient access and quality standards with respect to provision of genetic testing. However, while we agree that licensing does play some role in universal access, public health plans such as Medicaid and Medicare, as well as private payers, continue to be free to refuse coverage and payment even if every laboratory in the country offers a test. Moreover, in addition to such reimbursement policy, other factors, including practice patterns and professional talent distribution, also impact what tests are conducted in what regions of the country. Therefore, we do not support the assertion that in most cases gene patents have had a direct and overarching negative impact on the ability of a patient to obtain a test.

In terms of clinical access on behalf of patients, our assessment of the data suggests that clinicians are often significantly limited by contractual and financial barriers placed on them by their organization/institution or cost containment restrictions imposed by public and private payers. The ability for every laboratory to offer every test, in our view, is a commercial

objective more than a patient access issue since clinicians can and do order genetic tests for patients every day from laboratories both across the hall and across the county.

Nevertheless, we agree that the inability of certain populations to afford genetic testing is an important and valid concern and should be addressed directly as an integrated component of systemic health care reform. It is important that good intentions do not give way to negative outcomes in other parts of the health system or economy. As such, we would strongly encourage the Department of Health and Human Services ("HHS") to critically evaluate the criteria and requirements of all public health programs, including Medicare and Medicaid, to ensure that every beneficiary of public health funding has reasonable and timely access to genetic tests regardless of income or geographic location. In addition, we strongly encourage HHS to evaluate relevant laws, regulations and policies, such as anti-kickback, health care fraud statutes, and government reimbursement policies, that are overly burdensome or result in practical barriers on diagnostic companies who would otherwise elect to offer tests at little or no cost based on financial need.

We also agree that testing, including quality standards, whether by a single laboratory or multiple laboratories, are an important factor to the public's health. Test quality has been and should continue to be appropriately addressed by the Food and Drug Administration ("FDA") and the Center for Medicare and Medicaid Services ("CMS"). Specifically, those agencies should continue to work together to keep pace with laboratory and diagnostic innovation and identify new ways to evaluate proficiency, reliability, and reproducibility of new and innovative genetic tests. We do not believe, nor has FDA or CMS ever suggested, that there is any credible evidence that the quality of testing performed in sole source laboratories is routinely or demonstrably subpar in any way to that which is done in multiple laboratories. Nor do we believe that data indicate that modifying the gene patent system and protections it offers through exclusive licensee agreements would result in multiple laboratories performing proprietary tests with better quality than generated by current and developing oversight of quality assurance undertaken by these agencies and the laboratories themselves.

Finally, we believe that the determination of patentable subject matter and the protections afforded to such patentable subject matter should remain the primary function of the US Patent and Trademark Office, Congress, and the US courts. The suspension of patent protections such as exemptions from liability for patent infringement for a restricted class of innovation (gene patents), unless they are determined to be non-patentable (for instance, a court determination that they are a "product of nature"), is unwarranted and a risky intrusion in to a process that has delivered many key innovations to needy Americans.